Tuesday 2 September 2014

TRANSCATHETER AORTIC VALVE IMPLANTATION: WHAT'S NEXT?

4755 | BEDSIDE
Moderate to severe mitral regurgitation in patients undergoing trancatheter aortic valve replacement: a meta-analysis of mortality outcomes and mitral regurgitation evolution in 4,933 patients

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Purpose: Transcatheter aortic valve replacement (TAVR) is an effective alternative therapy in selected patients with severe aortic stenosis. We sought to investigate the role and effects of coexistent moderate to severe mitral regurgitation (sMR) in patients undergoing TAVR, which, to date, remain still unclear.
Methods and results: Sixteen studies enrolling 4,933 patients undergoing TAVR, including patients with sMR, were considered in the meta-analysis and analyzed for all-cause-mortality; a further meta-analysis was performed to assess MR evolution post TAVR. In patients with sMR, all-cause-mortality post TAVR was significantly increased, at 30-day (ES: -0.18; 95% confidence interval CI: -0.31 to -0.04, I2 = 46.51, Q = 7.48), 1-year (ES: -0.22; 95% CI: -0.36 to -0.08, I2 = 56.20, Q = 11.41) and 2-year-follow-up (ES: -0.15; 95% CI: -0.27 to -0.02, I2 = 0.00, Q = 2.64) compared to patients with absent or mild MR, independently from baseline left ventricular ejection fraction. Interestingly, sMR impact on outcome was statistically stronger when the CoreValve System was used. TAVR was associated with an improvement in MR entity, at 3/6-month (overall ES: -0.25, 95% CI: -0.41 to -0.09, I2 = 62.37, Q = 15.95) and at 1-year-follow-up (overall ES: -0.15, 95% CI: -0.28 to -0.01, I2 = 74.05, Q = 11.56), however this improvement reached significance only in patients undergoing TAVR with Edwards SAPIEN valve.
Conclusions: In patients undergoing TAVR, the presence of sMR increases post-procedural mortality. After TAVR, only the implantation of devices at higher positions significantly improved MR severity. Whether such recovery in MR severity impacts on mortality after TAVR remains to be defined.

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Increased mortality after transcatheter aortic valve implantation (TAVI) in patients with severe aortic stenosis and low ejection fraction: a meta-analysis of 6,898 patients

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Purpose: There is conflicting evidence regarding safety and efficacy of transcatheter aortic valve implantation (TAVI) procedures in patients with severe aortic stenosis and low left ventricular ejection fraction (EF). The primary aim of this study was to determine the impact of TAVI on short- and long-term mortality in patients with low EF (EF <50%); the secondary aim was to analyse the impact of TAVI procedure on EF recovery in the same setting of patients.
Methods and results: Twenty-six studies enrolling 6,898 patients with severe aortic stenosis undergoing TAVI procedure were included in the meta-analysis and analyzed for 30-day, 6-month and 1-year all-cause and cardiovascular mortality; a further meta-analysis was also performed in patients with low EF to assess EF changes post TAVI.
In low EF patients, both all-cause and cardiovascular short- and long-term mortality were significantly higher when compared to patients with normal EF (30-day-all-cause mortality: 0.13; 95% confidence interval [CI]: 0.01 to 0.25, I2 = 49.65, Q = 21.85; 1-year-all-cause mortality: 0.25; 95% [CI]: 0.16 to 0.34, I2 = 25.57, Q = 16.12; 30-day-cardiovascular mortality: 0.03; 95% [CI]: -0.31 to 0.36, I2 = 66.84, Q = 6.03; 1-year-cardiovascular mortality: 0.29; 95% [CI]: 0.12 to 0.45, I2 = 0.00, Q = 1.88). Nevertheless, in low EF patients TAVI was associated with a significant recovery of EF, which started at discharge and proceeded up to 1-year-follow-up.
Conclusions: Patients with low EF severe aortic stenosis have higher mortality following TAVI compared to normal EF patients, despite a significant and sustained improvement in EF.

4757 | BEDSIDE
Coronary artery disease significantly impairs long term outcomes after transcatheter aortic valve implantation

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Background and aims: Coronary artery disease (CAD) is frequent and negatively impacts the prognosis of patients with severe aortic stenosis (AS) who underwent surgical aortic valve replacement (SAVR). However, in patients with severe AS referred for TAVI the impact of CAD on outcomes has not been fully delineated. Furthermore, less is known about the indication and strategy for revascularization in these high risk patients. This study sought to determine in patients undergoing transcatheter aortic valve implantation (TAVI) the prevalence and prognostic impact of the presence of CAD as well as to access the safety and feasibility of percutaneous revascularization (PCI) before TAVI.
Methods: Patients who underwent successful TAVI from September 2007 to October 2012 were retrospectively divided into two groups according to the presence of CAD defined as the presence of prior coronary revascularization or at least one epicardial stenosis >50% on coronary angiography. In selected patients, PCI was performed before TAVI either in a planned intervention prior to TAVI (staged PCI) or at the time of TAVI (concomitant). Study outcomes included 30-day, 1-year and 2-year all-cause death plus the safety outcomes, defined according to the Valve Academic Research Consortium (VARC).
Results: Ninety-one patients were included and 46 (51%) had coexisting CAD. Patients with CAD were more frequently men, hypertensive, dyslipidemic, had worse glomerular filtration rate (GFR) and more left ventricular dysfunction. Mean EuroScore 2 was significantly higher in CAD group. PCI was performed in 13 patients (28%). There were no more significantly adverse events in patients who underwent PCI before TAVI than in patients who underwent TAVI alone. The 30-day mortality were similar between CAD and non-CAD patients (9% and 5% respectively, p=0.442), but at long-term the rates of death were significantly higher in CAD group (hazard ratio with CAD of 2.2; 95% CI from1.2 to 4.6, p=0.042), at 1 year were 26% in CAD patients and 14% in no-CAD patients, and at 2 years were 50% in CAD patients and 24% in non-CAD patients (Kaplan-Meier analysis).
Conclusions: In severe symptomatic AS who underwent TAVI, CAD is frequent and adversely impacts long-term outcomes, but not procedure outcomes. In selected patients, PCI before TAVI appears to be feasible and safe.

4758 | BEDSIDE
Feasibility and outcomes of transcatheter aortic valve implantation in high-risk patients with stenotic bicuspid aortic valves

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Aims: Bicuspid aortic valve (BAV) is the most common congenital heart disease and may lead to aortic valve stenosis. Although Transcatheter Aortic Valve Implantation (TAVI) emerged as an alternative therapy in high-risk patients with tricuspid aortic valve stenosis, presence of a stenotic BAV is often considered a contraindication, due to its unique anatomy and increased risk of periprocedural complications. We aimed to assess the feasibility and outcomes of TAVI in high-risk patients with bicuspid aortic valve stenosis.
Methods: The study is a prospective, single-centre registry of patients with BAV stenosis treated with TAVI. Periprocedural safety, hemodynamic and clinical outcome was observed during patient follow-up.
Results: Of 120 high-risk patients with severe aortic stenosis who underwent TAVI from January 2009 to January 2014 in our centre, 15 (12.5%) patients had documented BAV. Patients were aged 76±9 years (range 56-90), with mean Logistic EuroScore I of 20±11%, all in New York Heart Association functional class III. The mean aortic valve area was 0.76±0.36 cm^2, mean gradient was 45.3±15.1 mmHg and mean LVEF was 50.5±12.4%. The procedure was performed using transfemoral access in 13 (87%), transaortic in 1 (6.5%) and transapical in 1 (6.5%) patient. Medtronic CoreValve prosthesis was implanted in 9 (60%) and Edwards Sapien XT in 6 (40%) patients. TAVI procedure was successful in 13 patients (87%). Major adverse events according to the second Valvular Academic Research Consortium definitions were present in 2 patients: 1 periprocedural death (Edwards Sapien XT 29) and 1 periprocedural stroke (Medtronic CoreValve 26). Importantly, both complications were related to prosthesis dislocation from the bicuspid aortic valve annulus. Postprocedural aortic valve mean gradient was 8±2 mmHg and AVA 1.4±0.4 cm^2. After a mean follow-up of 13±12 months (range 1-39) no further adverse events occurred. All survivors remained in NYHA class I or II.
Conclusions: Our initial experience suggests TAVI using CoreValve and Sapien XT prostheses in high risk patients with stenotic bicuspid aortic valve is feasible, leading to good short term hemodynamic and clinical improvement. However, prosthesis dislocation during implantation carries ominous prognosis warranting further multicentre studies on BAV anatomy and prosthesis matching for this specific group of patients.

4759 | BEDSIDE
Neurological damage after TAVI versus aortic valve replacement in patients with similar EuroScore

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Purpose: There are no studies comparing the incidence of acute silent cerebral ischemic lesions and neurocognitive dysfunction following TAVI vs. conventional aortic valve replacement (AVR) in contemporary patients with comparable surgical risk.
Methods: Fifty consecutive patients (p) undergoing TAVI were compared to 48 contemporary p with log EuroScore (ES) >10% undergoing AVR. Diffuse weighted Magnetic Resonance Imaging (MRI) was performed in 71 p (40 TAVI and 31 RVA; mean time after intervention 7 days) to evaluate acute cerebral damage. A comprehensive neurocognitive assessment was performed at baseline and at 3 months by a neuropsychologist in 55 p (34 TAVI and 20 RVA) following the recommendations of the "Statement of Consensus on Assessment of Neu-

robehavioural Outcome After Cardiac Surgery". Potential cognitive decline from baseline was determined using the Reliable Change Index (RCI).
Results: Both groups were comparable concerning age (TAVI median age 80 y vs. 79 y in AVR, p=0.8) and Log ES (15.2±12.7 in TAVI vs 14.4±5.6 in AVR, p=0.72). Twenty-nine of 71 p (40.8%) had new ischemic lesions in post-intervention MRI images, 18 (45%) in TAVI group vs 11 (35.5%) in AVR group (p=0.47), consistent with cerebral embolization. Mean ischemic volume and number of lesions were similar in both groups (median volume (Q1-Q3) 350 mm^3 (126-872) in TAVI vs 274 mm^3 (127-996) in AVR, p=0.98; median of 2 lesions in TAVI vs. 2 lesions in AVR, p=0,124). Multivariate analysis showed that absence of previous anticoagulant treatment and age were independent risk factors of new cerebral lesions. RCI showed cognitive decline in 16 out of 55 p (29.1%) assessed, 9 out of 34 p (25%) in TAVI and 7 out of 20 p (35%) in AVR group (p=NS). Cognitive decline was not considered to have clinical relevance after expert assessment. There was no correlation between the volume of ischemic lesions and neurocognitive decline.
Conclusions: In patients with comparable surgical risk the rate of silent ischemic foci detected by DW-MRI after TAVI and after AVR was similar. Neurocognitive decline is not clinically relevant after both techniques and it does not correlate with the size and number of cerebral ischemic lesions.

4760 | BEDSIDE
To predilate or to not predilate in transcatheter aortic valve implantation? Single-center experience with self-expandable devices

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Objectives: The aim of this study was to compare the outcomes of transcatheter aortic valve implantation (TAVI) with a CoreValve Revalvivng System with or without preparatory balloon aortic valvuloplasty (PBAV).
Methods: From November 2007 to September 2013 all patients treated with MCV were included in this analysis. Patients were divided in 2 groups: those where PBAV was performed and those where MCV wasdirectly implanted. PBAV was performed according to operator descretion, after consideration of patient anatomical characteristics. Outcomes were assessed according to valvular academic research consortium (VARC-2) criteria at 30 days and 1 year.
Results: Of 538 patients that underwent TAVI in our center, 206 were treated with a MCV via one of the available access routes. Of those, 133 underwent PBAV, while 73 direct valve implantation. Baseline characteristics between the 2 groups were similar. At 30 days there were no significant differences in all-cause and cardiovascular mortality (3% vs. 5.5%, p=0.380; and 1.5% vs. 5.5%, p=0.105; respectively). A trend for a higher incidence of cardiac tamponade (2.4% vs. 7.8%; p=0.078) and a significantly higher rate of at least moderate peri-prosthesic aortic regurgitation (PPAR) requiring valvular balloon post-dilation (VBPD; 35.6% vs. 49.3%, p=0.056) was noted amongst patients where PBAV was not performed. Conversely patients who underwent PBAV had more AKI (32.3% vs. 19.4%; p=0.049). No significant differences were observed in PPAR, peri-procedural cerebrovascular events, and 30-day or 1-year VARC-2 composite endpoints between the 2 groups. Finally, at a median follow-up period of 429 days (IQR 208 - 730), Kaplan-Meier curves reported no significant differences in long-term all-cause (17.8% vs. 23%; Log Rank p=0.210) and cardiovascular mortality (13.3% vs. 17.6%; Log Rank p=0.256).
Conclusion: In the present study, direct implantation of MCV without PBAV did not decrease the incidence of procedural complications and was not associated with improved survival. Conversely it was associated with a greater incidence of post-implantation complications and a higher rate of VBPD.

4761 | BEDSIDE
Transcatheter aortic valve implantations after previous coronary artery bypass grafting: insights from the FRANCE 2 registry

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Background: Previous coronary artery bypass grafting (CABG) increases operative risk for conventional valve replacement. Transcatheter aortic valve implantation (TAVI) has been shown to be successful in high risk subgroups of patients. In patients undergoing TAVI, we aimed to compare procedural outcomes and overall survival according to whether or not they had previous CABG.
Methods: From January 2010 to December 2011, among the 3761 patients selected to undergo TAVI in 34 centers of our country, 683 patients (18%) had a history of CABG. Outcomes were prospectively collected according to the Valve Academic Research Consortium (VARC) criteria.
Results: Patients with previous CABG were younger, higher rates of diabetes and vascular disease, higher logistic EuroScore (29.8±16.4 vs 20.1±13.0, p<0.001) but lower rates of pulmonary disease. The two types of valves (Edwards SAPIEN and Medtronic CoreValve) were equally implanted in the two groups. VARC complications were similar in patients with compared to patients without previous CABG, as well as 30-day and 1-year mortality (9.2% vs 9.7%; p=0.71; and 19.0% vs 20.2%; p=0.49, respectively). Using multivariate analysis, CABG was not associated with higher1-year mortality after TAVI.
Conclusion: Previous CABG does not adversely impact outcomes in patients undergoing TAVI. This result shows that TAVI might be an alternative to surgery by the heart teams in high-risk patients with severe aortic stenosis and previous CABG.

4762 | BEDSIDE
Correlation of corevalve implantation depth with the observed post implantation aortic regurgitation and its impact on necessity for additional intraprocedural techniques

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Purpose: Procedural technical features of CoreValve implantation have been shown to affect the short and long-term outcome after Transcatheter Aortic Valve Implantation (TAVI). The aim of this study was to evaluate the impact of CoreValve implantation depth on the short-term hemodynamic and procedural characteristics.
Methods: From June 2008 until February 2013, patients who had undergone TAVI with the CoreValve device, were retrospectively studied. The device implantation depth was evaluated in offline analysis by measuring the distance between the lowest coronary cusp calcium border, as depicted in the post-implantation aortography, and the lowest edge of the device frame (smaller measured distance indicating higher implantation depth, see image). The aortic valve regurgitation (AR) was evaluated after TAVI and classified as none, mild and severe. Finally, the necessity of post-implantation balloon dilatation in order to achieve a better valve expansion was recorded.
Results: A total of 119 patients (mean age 80.6±5.3 yrs, 62 males) were finally enrolled. The implantation was performed either transfemoraly, or through subclavian route (12 patients). A statistically significant difference was found for the implantation depth between the three post-TAVI aortic regurgitation classifications (8.12mm for none AR, 7.95mm for mild and 6.27mm for severe AR, p=0.046), indicating increased AR with higher device implantation. Similarly, patients who underwent balloon post-dilatation, had statistical significant higher implantation depth compared with those who didn't (6.39±3.2mm vs 8.14±2.5mm, p=0.012). The implantation depth remained an independent predicting factor of balloon post-dilatation necessity in multivariate logistic regression [OR: 0.775 (0.64-0.938), p=0.009].
Conclusions: The CoreValve device implantation depth is strongly correlated with the post-implantation observed aortic regurgitation, as well as with the necessity of balloon post-dilatation. It seems that, concerning hemodynamic short-term outcome, operators should be even more careful in device implantation depth ensuring the optimal positioning.

4763 | BEDSIDE
Transcatheter valve-in-valve implantation for degenerated bioprosthetic aortic valves: insights from the FRANCE 2 registry

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Background: The operative mortality associated with repeated heart valve surgery is higher than the initial valve operation. Transcatheter aortic valve implantation (TAVI) has been shown to be successful in high-risk subgroups of patients. We aimed to evaluate the impact of previous aortic valve surgery on procedural outcomes and overall survival in patients undergoing TAVI in surgical bioprosthetic aortic valve (VIV).
Methods: 3761 consecutive patients underwent a TAVI in 34 French centers; among them, 64 patients (1.7%) had a previous bioprosthetic aortic valve and underwent VIV procedure. Baseline clinical and echocardiographic data were available in all patients. Outcomes were prospectively collected according to the Valve Academic Research Consortium (VARC) classification.
Results: In the 64 patients with VIV procedure, two types of valves were implanted: Edwards SAPIEN (48.4%) and Medtronic CoreValve (51.6%). Compared to the 3697 patients with no previous surgical bioprosthetic aortic valve, patients with VIV were younger, more symptomatic (85% were NYHA class III or IV) and they had more previous coronary artery bypass grafting, less peripheral vascular disease and a higher EuroSCORE (33.6±17.5 vs 21.7±14.0 p<0.001). Procedural characteristics were similar. No significant differences were observed in the incidence of VARC-defined complications. The presence of a previous bioprosthetic aortic valve was not a factor of higher 1-year mortality. At 1 year, 89.5% of surviving patients were NYHA class I or II in the VIV patients.

Conclusion: Previous bioprosthetic aortic valve does not adversely impact outcomes in patients undergoing TAVI. This result should be taken into account by the heart teams to consider VIV as an alternative option for the management of bioprosthetic valve failure in high-risk patients.

4764 | BEDSIDE
Prosthesis choice for transcatheter aortic valve replacement: improved outcomes with the adoption of a patient-specific transcatheter heart valve selection algorithm

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Purpose: Transcatheter aortic valve replacement (TAVR) is routinely performed by using either self-expanding or balloon-expandable prosthesis, which are the most widely used TAVR devices. No specific indications for these two valves have been adopted so far. This study prospectively investigated the impact of a patient-specific transcatheter heart valve (THV) selection algorithm on TAVR outcomes.
Methods: Consecutive patients who underwent TAVR using the selection algorithm (Figure 1) since January 2012 (N=184) were compared with earlier consecutive patients in whom the algorithm was not applied (N=193). The primary endpoints were: 1) VARC-defined device success and 2) paravalvular regurgitation (PVR)≥moderate.
Results: Patients in the study group were more likely to have diabetes mellitus (35.3% vs. 24.9%, p=0.027) and renal insufficiency (35.3% vs. 18.5%, p<0.001), whereas COPD was more frequent among the control group (28.4% vs. 39.3%, p=0.027). Device success was obtained in 87.0% of patients included in the study group and in 77.2% of those included in the control group (adjusted OR: 1.85, 95%CI 1.03-3.31, p=0.039). On echo, PVR≥moderate was present in 5.6% of the study group and in 17.4% of the control group (adjusted OR: 0.35, 95%CI 0.16-0.76, p=0.008).

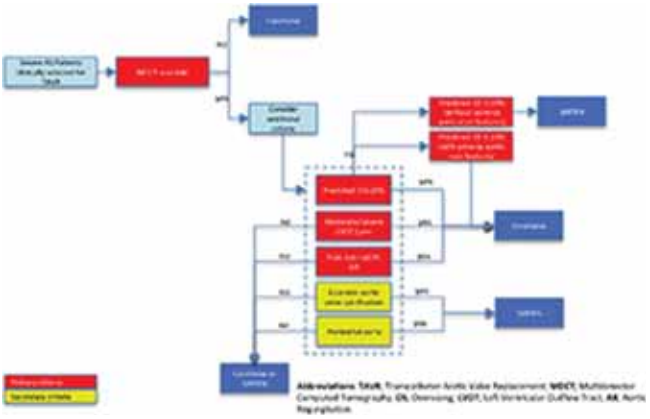

Figure 1. THV selection algorithm.

Conclusions: The implementation of a patient-specific THV selection algorithm for TAVR, which entails a specific THV implantation (CoreValve or SAPIEN XT) for specific aortic root anatomies, may improve clinical outcomes after TAVR by allowing higher device success and reducing the incidence of more than mild PVR.

INNOVATION AND THE HEART 2

4765 | SPOTLIGHT
Association of systolic blood pressure levels with cardiovascular events and all-cause mortality among older adults without antihypertensive medication

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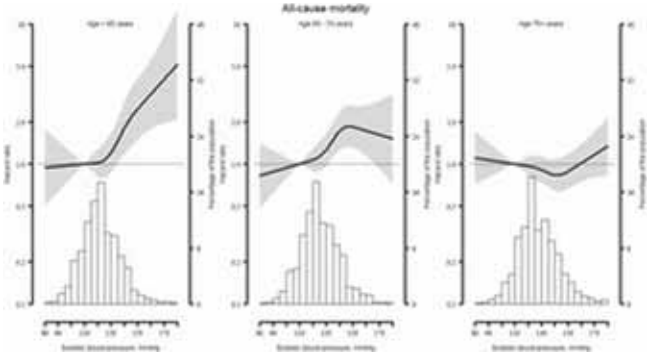
There are very limited data on the optimal levels of blood pressure (BP) in elderly individuals without hypertension. Therefore we aimed to identify the optimal BP in elderly persons not taking antihypertensive medication.

10,983 participants without hypertension, enrolled in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort study were categorized into 3 age groups: 55-64, 65-74 and ≥75 years old. All groups were further divided according to baseline SBP levels: <120 (reference group), 120-129, 130-139, 140-149, and >150 mmHg. Four main outcomes were analysed in the study: CVD, CHD and stroke incidence, and all-cause mortality rate. Median follow-up was 4.5 years for CVD and CHD, 5.7 years for stroke, and 6.0 years for all-cause mortality.
After multivariable adjustment, there was a linear relation between SBP and the risk of CVD and CHD incidence, and all-cause mortality rate with the highest risk for SBP≥140 mmHg among participants aged 55-64 and 65-74 years (HR 3.06, 95%CI: 1.54-6.09; p=0.003 and 1.85, 95%CI: 1.03-3.33; p=0.017 for CVD incidence, 4.10; 95%CI: 1.86-9.06; p=0.003 and 2.37, 95%CI: 1.17-4.80; p=0.014 for CHD incidence, and 2.66, 95%CI: 1.61-4.39, p=0.001 and 1.87, 95%CI: 1.32-2.65; p<0.001 for all-cause mortality, respectively). No relation between SBP and CVD and CHD incidence, and all-cause mortality rate was observed for persons aged ≥75 years. The linear relation between SBP and stroke was observed only for patients ≥75 years, with the highest risk for SBP≥140 mmHg (3.52, 95%CI: 1.72-7.22; p<0.001).



The results suggest a hypothesis that for all individuals at age between 55-74 years old the recommended level of SBP should be <140 mmHg if tolerated, and due to significant stroke reduction it should be also considered for the oldest patients.

4766 | SPOTLIGHT
Aripazine reverses unfractionated and low molecular weight heparins, fondaparinux and new Xa and IIa oral anticoagulants: report of Phase I/II clinical trial with edoxaban

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Purpose: Aripazine (PER977) is a small molecule designed to bind unfractionated and low molecular weight heparins (UFH, LMWH), fondaparinux, and the new oral anticoagulants (NOACs). Its non-covalent binding to anticoagulants prevents them from binding to their endogenous targets, reversing their anticoagulation. Aripazine is ready for intravenous injection; has no significant toxicity effects in animals at clinical doses; no affects on CYP metabolism; and no drug-drug binding. In animals anti-coagulated with NOACs (both Xa & IIa) or UFH or LMWH, aripazine restores normal hemostasis in rat tail transection and liver laceration bleeding models. Moreover, aripazine reduced bleeding when given immediately after an induced injury in NOAC anticoagulated rats.
Methods: A first in human, 7 cohort, 2 period, ascending dose (5–300 mg) trial with aripazine alone and after 60 mg edoxaban was completed in volunteers.
Results: Aripazine alone showed no serious adverse events and no procoagulation signal (D-dimer, F1.2, TFPI). At 50-300 mg doses, aripazine reversed the anticoagulation of 60 mg edoxaban with no evidence of rebound over 24 hrs (Fig. 1). Aripazine also restored normal clot formation and fibrin integrity within the clot, which had been altered with edoxaban therapy, as shown by scanning electron micrographs.

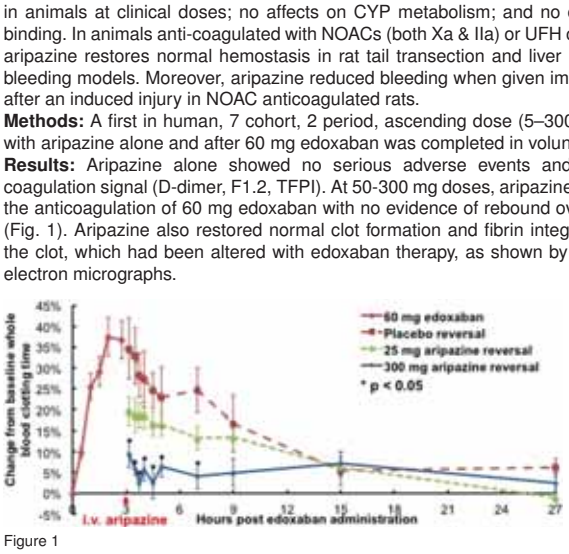

Figure 1

Conclusions: Aripazine is safe and well tolerated at doses that reverse the an-

ticoagulation of therapeutic edoxaban. In preclinical studies, aripazine also reverses the anticoagulant effect of other NOACs as well as UFH, LMWH and fondaparinux suggesting it should have similar effects in humans. Its advantages include small size, unlikely immunogenicity; single bolus injection; quick onset (10 minutes); prolonged effects; quick metabolism and renal clearance.

4767 | SPOTLIGHT
Duration of prehospital resuscitation efforts and neurologically intact survival after out-of-hospital cardiac arrest

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Background: During out-of-hospital cardiac arrest, it is unclear how long prehospital resuscitation efforts should be continued. We investigated the relationship between neurologically intact survival and the time interval from collapse to achievement of return of spontaneous circulation (ROSC) through prehospital resuscitation efforts stratified by initial cardiac arrest rhythm.
Methods: From the All-Japan Utstein Registry, a prospective, nationwide, population-based registry of out-of-hospital cardiac arrest between 2005 and 2011, we identified 31845 adult patients who achieved ROSC through prehospital resuscitation efforts after witnessed out-of-hospital cardiac arrest. We calculated the collapse-to-ROSC interval. The primary endpoint was favorable 30-day neurological outcome.
Results: Of the 31845 study patients, 11621 (36.5%) had an initial rhythm of ventricular fibrillation/pulseless ventricular tachycardia, 12965 (40.7%) of pulseless electrical activity and 7259 (22.8%) of asystole. Overall, 8714 (27.4%) had favorable neurological outcome. After adjustment for confounders, longer collapse-to-ROSC interval resulted in worse neurological outcome (adjusted OR, 0.94; 95% CI, 0.94-0.94; $P<0.001$). In non-linear regression analyses for each initial rhythm category, the likelihood of favorable neurological outcome decreased with every minute the collapse-to-ROSC interval increased ($P<0.001$, respectively). Sensitivity for favorable neurological outcome was 99% or more when ROSC was achieved within 38 minutes for ventricular fibrillation/pulseless ventricular tachycardia, within 37 minutes for pulseless electrical activity and within 42 minutes for asystole. The collapse-to-ROSC interval associated with both 100% sensitivity and negative predictive value for favorable neurological outcome ranged from 56 minutes for asystole to 58 minutes for ventricular fibrillation/pulseless ventricular tachycardia. Subgroup analyses examining quartiles of age and presence or absence of bystander resuscitation produced similar intervals.
Conclusions: Prehospital resuscitation efforts should be continued for at least 37 minutes to achieve 99% or more sensitivity for neurologically intact survival after witnessed out-of-hospital cardiac arrest irrespective of initial cardiac arrest rhythm.

4768 | SPOTLIGHT
Cardiorespiratory fitness attenuates the progression from mormal blood pressure to resistant hypertension

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Purpose: To assess the association between exercise capacity and the progression to resistant hypertension in individuals with normal blood pressure (BP) at baseline.
Methods: From 1990 to 2012, 11,475 apparently healthy individuals underwent an exercise stress test (GXT) at the Veterans Affairs Medical Center, Washington, DC. We identified 8,220 individuals (mean age: 57±12) with normal blood pressure prior to GXT. We established four fitness categories based on the age and MET level achieved. Individuals with a peak MET level within the 20th percentile (4.2±0.8 MET) comprised the Least-Fit category (n=2,101). Those who achieved a MET level between the 26st and 50th percentile (6.2±0.6 MET) comprised the Low-Fit category (n=2,512), those with a peak MET level between 51% and 79% (8.0±0.5 MET) comprised the Moderate-Fit (n=2,056) and those ≥80th percentile (10±1.0 MET), comprised the High-Fit category (n=1,551). Resistant hypertension is defined as BP >140/90 mm Hg despite the concurrent use of 3 antihypertensive agents of different classes prescribed at optimal dose amounts, preferably one of them diuretic.
Results: During the follow-up time of 19±6.2 years, 611 individuals (7.5%) developed resistant HTN. After adjusting for age, body mass index (BMI), cardiovascular (CV) disease CV risk factors, muscle-wasting disease and cardiac medications, the rate of progression to resistant hypertension was 42% lower for individuals with an exercise capacity ≥9 METs (hazard ratio=0.58; CI: 0.44-0.92; p=0.016).
Conclusion: Exercise capacity ≥9 METs attenuated the rate of progression to resistant HTN in veterans.

4769 | SPOTLIGHT
Implications of american and european guidelines for cardiovascular disease prevention: the rotterdam study

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Background: Recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines have generated concerns regarding inferences and accuracy of risk models in cardiovascular disease (CVD) prevention. We aimed to determine implications of the ACC/AHA, the Adult Treatment Panel-III (ATP-III) and the European Society of Cardiology (ESC) guidelines in a prospective cohort of individuals ≥55 years.
Methods: The study comprised 4,854 participants (mean-age 65.5 years) from the Rotterdam Study. We calculated 10-year risks for hard atherosclerotic CVD including coronary heart disease (CHD) and stroke using the pooled cohort equation (ACC/AHA); hard CHD by the ATP-III estimates; and CVD mortality using the Systematic COronary Risk Evaluation (SCORE) equation. We computed the proportion of participants recommended for drug treatment based on the 3 guidelines and examined calibration of the 3 risk models underlying the recommendations.
Results: Mean age of the participants was 65.5 years. The ACC/AHA guidelines recommended all men and 81% of women as candidates for drug treatment. The inferences were 67% of men, 49% of women for the ATP-III and 97% of men, 90% of women for the ESC guidelines. All 3 algorithms overestimated the risk. The average predicted vs. observed risks were 18.9% vs. 11.4% (men), 10.0% vs. 6.8% (women) using the ACC/AHA; 15.8% vs. 6.8% (men), 5.4% vs. 3.2% (women) for the ATP-III; and 6.8% vs. 3.7% (men), 3.9% vs. 2.1% (women) using the SCORE equation.
Conclusions: All men and more than 80% of women ≥55 years were candidates for drug treatment based on both American and European guidelines. The ACC/AHA algorithm, as well as the ATP-III and SCORE functions, systematically overestimated the risk.

4770 | SPOTLIGHT
Ideal cardiovascular health is associated with favorable cardiac remodeling and lower incidence of heart failure in the Framingham Offspring Study

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Background: The American Heart Association (AHA) has defined the ideal cardiovascular health (Life's Simple 7TM) in an effort to promote its AHA 2020 Strategic Impact Goal of reducing cardiovascular mortality and increasing cardiovascular health by 20% by the year 2020. Limited data suggest that the AHA Heart Healthy score (AHA score) is inversely related with the incidence of cardiovascular disease (CVD). It is unknown whether an ideal AHA score also lowers the risk of heart failure, and whether cardiac remodeling plays a key mediating role underlying any potential association.
Methods and results: We investigated the relations between the AHA Score and cardiac remodeling cross-sectionally and the incidence of heart failure prospectively in up to 3200 Framingham Offspring Study participants (mean age 59 years, 53% women). We hypothesized that the AHA score is inversely associated with heart failure incidence, mediated in part by the favorable effect of an ideal score on echocardiographic indices of cardiac remodeling, including left ventricular (LV) mass (LVM), left atrial dimensions (LAD), and fractional shortening (FS). Adjusting for age and sex, an ideal AHA score (non-smoking status, ideal body mass index, regular physical activity, healthy diet, and an optimal profile of total serum cholesterol, blood pressure, and glucose; range of AHA score: 0-7, with 7 representing ideal status) was associated with lower LVM and LAD (beta estimates -5.26 gm and -0.06 cm, respectively per unit-increase in AHA score; $p<0.0001$ for both) but was not related to FS ($p>0.05$). In additional analyses, the AHA score was also inversely associated with the two components of LVM, i.e., LV diastolic dimensions (LVDD) and LV wall thickness (beta estimates -0.02 cm and -0.04 mm, respectively, $p<0.05$). Additionally, the incidence of HF was inversely related with the baseline AHA score in age- and sex-adjusted models (188 events over 16 years, Hazards ratio [HR] 0.74 per unit-increase of AHA score, 95% CI 0.66, 0.84), an association that was slightly attenuated upon adjustment for LVM (HR 0.82 per unit-increase of AHA score, 95% CI 0.70, 0.96).
Conclusion: Our findings in a large community-based sample emphasize the impact of an ideal cardiovascular health on cardiac remodeling indices and on heart failure risk, underscoring the public health opportunities to prevent heart failure by promoting a healthier lifestyle.

4771 | SPOTLIGHT
Interleukin 13 receptor alpha 1 regulates the development of metabolic syndrome and cardiomyopathy in mice

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Aims: Increasing evidence suggests that chronic low-grade inflammation that accompanies metabolic disorders such as obesity, insulin resistance, and type-2 diabetes mellitus, may also be linked to the induction and progression of cardiovascular disease (CVD). Although the role of pro-inflammatory cytokines in CVD has received much attention, the possible role of anti-inflammatory cytokines remains unexplored. Interleukin 13 (IL-13) is a Th-2 mediated anti-inflammatory cytokine that exerts its effects through the interleukin 13 receptor α1 (IL-13Rα1) sub-unit. Thus, we aimed to investigate the potential role of IL-13Rα1 in metabolic syndrome and CVD using a genetically-engineered mouse model.
Methods and results: IL-13Rα1-deficient mice (Il13ra1–/–) developed several metabolic syndrome features: obesity, high fasting glucose, impaired response to glucose tolerance test, and higher total cholesterol levels. Il13ra1–/– mice displayed significantly lower TNF-α and undetectable IL-1β plasma concentrations, ruling out the possibility that the observed phenotype is due to an underlying elevation of pro-inflammatory cytokines. LacZ reporter staining demonstrated that IL-13Rα1 is expressed in the heart. Thus, we assessed the role of IL-13Rα1 in cardiac function and structure using echocardiography. Il13ra1–/– mice developed significant systolic dysfunction, which progressed to LV dilatation and posterior wall thinning at the age of 6 months. Furthermore, Il13ra1–/– mice displayed decreased expression of STAT 3, TGF-β and IGF-1 genes that regulate cardiac growth and extracellular matrix deposition. Strikingly, a high-fat diet improved remodelling and dysfunction in Il13ra1–/– mice, suggesting that the cardiomyopathy was independent of the metabolic syndrome. Next, to evaluate the role of IL-13Rα1 in cardiac remodelling, transverse aortic constriction (TAC) was performed. Remarkably, echocardiography imaging performed 1 and 3 weeks after TAC showed that Il13ra1–/– mice demonstrated a lesser degree of cardiac hypertrophy and did not develop cardiac interstitial fibrosis compared to controls.
Conclusions: Our findings show, for the first time, that IL-13Ra1 is expressed in heart tissue and regulates the development of metabolic syndrome and dilated cardiomyopathy, the latter being associated with crucial changes in extracellular matrix deposition. Thus, IL-13Ra1 may represent a novel biomarker and therapeutic target for these serious cardiovascular disorders.

4772 | SPOTLIGHT
Weight change is associated with an increase in mortality risk

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Purpose: Recent findings from clinical cohorts suggest that overweight and obese individuals have a better prognosis than normal weight subjects, a phenomenon termed as the "obesity paradox." However, relatively little is known about the effects of weight change (gain or loss) in this association. Thus, the purpose of this study was to determine the mortality risk association between weight and body mass index (BMI) changes.
Methods: From 1989 to 2011, we identified 60,972 veterans (54,569 men and 6,402 women; mean age 62$\pm$16) with at least two weight assessments at least 6 months apart. Risk factors, medications and mortality status information were extracted from the electronic records. The follow-up period was 9.8$\pm$4.5 years (597,078.75 person-years). Initial and final BMI was calculated based on the respective weight (kg) and height (m) of each participant. We formed the following five weight groups based on weight change (initial-final) per year of follow-up: Weight change $\pm\leq$2.5% (Referent); weight increase of 2.6%-5.0%; weight increase $>$5%; weight decrease of 2.6-5%; and weight decrease $>$5%. We also formed five BMI-change groups, based on similar percentages of BMI changes. Cox proportional hazard models were then used to compare risks between the weight and BMI groups using the group with no change as the reference group.
Results: There were a total of 12,771 deaths for an annual mortality rate of 2.2% per 1,000 person-years. Cox proportional hazard analysis adjusted for age, medications, year of initial weight assessment, cardiac risk factors, cardiac medications, cancer, kidney failure, and HIV/AIDS revealed that change in weight or BMI were associated with increased risk of mortality for the entire cohort and within the traditional BMI categories. The increase in risk was graded and was more pronounced (about 2-fold) with weight losses compared to weight gains. Specifically, weight increase of 2.5% to 5% was associated with 40% increase in risk (hazard ratio: 1.40; CI: 1.30-1.52), while the risk for of the same magnitude decrease in weight was 3-fold (hazard ratio: 3.0; CI: 2.90-3.20). The risk was similar to the changes observed in BMI. The trend in risk was similar when weight changes were examined within the traditional BMI categories.
Conclusions: Weight changes are associated with increased mortality risk. The risk was more pronounced with weight losses than weight gains, for the entire cohort and within the traditional BMI categories.

4773 | SPOTLIGHT
The clinical utility of the novel endothelium-derived biomarker C-type natriuretic peptide for predicting myocardial infarction in the general community

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Purpose: Identifying subjects at risk for cardiovascular (CV) events in a community-based setting is a high priority and highlights the need to find specific biomarkers for underlying CV disease in such subjects. C-type natriuretic peptide (CNP) is an endothelial cell derived peptide that has been shown to possess vasculo-protective properties. CNP is a coronary vasodilator, is pro-angiogenic secondary to ischemic insult and is activated in the coronary vascular wall in humans with coronary artery disease (CAD). While we and others have reported that CNP circulates, no studies have assessed the prognostic utility of plasma CNP for CV events in the general community. We hypothesized that elevated CNP will have significant and added prognostic value for myocardial infarction (MI) in subjects from the general community.
Methods: Plasma CNP was assessed in 1,841 subjects randomly selected from a general community of our country, MN. Subjects were followed for MI, heart failure (HF), death and cerebrovascular accidents (CVAs) over 12 years. Hazard ratios (HRs) for CNP in the highest quartile (compared to lower three quartiles) were calculated, both unadjusted and with adjustment for standard risk factors (RFs; i.e. age, sex, BMI, cholesterol, creatinine, smoking, presence of diabetes, CAD and hypertension). Statistical significance: $P<0.05$.
Results: Mean age of our cohort was 62$\pm$11yrs and 48% were male. Median (Q1,Q3) plasma CNP was 13.2 (10.2, 16.8) pg/ml and the highest quartile of CNP corresponded to values of $>$16.8 pg/ml. Over the 12 yr follow-up, 189 MI, 232 HF, 328 deaths and 350 CVAs were recorded. Cox modeling demonstrated that CNP in the highest quartile has prognostic significance for MI, HF and death (HRs 1.88, 95% CI 1.40-2.51; 1.76, 95% CI 1.35-2.30 and 1.41, 95% CI 1.12-1.78, respectively), but not CVA. With adjustment for standard RFs, the highest CNP retained prognostic significance for MI and HF (HRs 1.67, 95% CI 1.24-2.26 and 1.47, 95% CI 1.12-1.94 respectively), but not death. Integrated discrimination analysis suggested that addition of highest CNP to standard RFs significantly improved the prediction of MI by 9%, but not HF.
Conclusion: We report for the first time that elevated plasma CNP, in subjects from the general community, has prognostic significance and adds value to standard RFs, for MI, but not HF, death, or CVA. Our findings advance the clinical value of the endothelium-derived peptide, CNP, as a novel plasma biomarker for the identification of subjects from the general community at risk for MI whom may benefit from preventative MI therapies.

NOVEL MECHANISMS TO CONTROL CARDIAC METABOLISM

4786 | BENCH
Moderate SirT1 overexpression during high fat diet preserves glucose tolerance and mitochondrial function

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Background: High fat diet is known to affect glucose handling and mitochondrial function under various conditions. The protein deacetylase SirT1, a known longevity factor, improves insulin sensitivity and affects mitochondrial biogenesis.
Objective: We assessed the influence of high fat diet on glucose handling, cardiac and mitochondrial function in wild type and hemizygote transgenic SirT1 mice.
Methods: Wild type (wt) and hemizygote SirT1 transgenic mice at 8 weeks of age were exposed either to high fat diet (HFD – 60% cal. from fat) or standard chow (SD). After 8 weeks of HFD, cardiac function was assessed by echocardiography and respiratory capacity of isolated mitochondria was measured. Furthermore, glucose tolerance was investigated with a glucose tolerance test (GTT) and insulin signalling of several organs was assessed with Western blot. SirT1 protein expression was also assessed.
Results: In contrast to wild type mice SirT1 transgenic mice had 2-fold higher SirT1 protein level in heart and skeletal muscle but otherwise displayed normal phenotype. Eight weeks of HFD resulted in increased body mass and epididymal fat weight in both, wild type and SirT1 mice. This weight gain was significantly less pronounced in SirT1 mice. Echocardiography revealed normal cardiac morphology, systolic and diastolic function with HFD. Cardiac mitochondrial function, as assessed by respiratory capacity, was unchanged between wild type and SirT1 mice. Eight weeks of HFD reduced respiratory capacity in wild type mice by -30%. In contrast, HFD in SirT1 mice resulted in an increase of respiratory capacity by +41% (glutamate: wt-SD 688$\pm$62 vs. wt-HFD 483$\pm$116 vs. SirT1-SD 535$\pm$85 vs.

SirT1-HFD 771±90 natomsO/min/mg). HFD led to impaired glucose tolerance in wt and SirT1 mice. However, SirT1 mice displayed improved glucose tolerance and lower maximal blood glucose levels during GTT than wt (AUC: 1228±101 vs. 1913±95 vs. 1158±92 vs. 1569±104). Insulin response as assessed by insulin stimulated P-Akt/Akt ratio was decreased in heart and skeletal muscle of wild type mice after HFD. In transgenic SirT1 mice, this loss of insulin sensitivity was not present.
Conclusion: A moderate overexpression of SirT1 improves insulin sensitivity and preserves mitochondrial function with short term high fat diet.

4787 | BENCH
Transient hyperglycemia induced persistent cellular senescence in human umbilical vein endothelial cells via SIRT1/p300/p53/p21 pathway

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Transient hyperglycemic exposure has been implicated to induce persistent endothelial dysfunctions, a phenomenon also known as 'metabolic memory'. Although metabolic memory has been demonstrated to promote microvascular endothelial senescence, whether it enhances macrovascular endothelial senescence remains obscure. Human umbilical vein endothelial cells (HUVECs) were incubated with normal glucose (5 mM) for 6 days, high glucose (30 mM) for 6 days, or high glucose for 1 days followed by normal glucose for 5 days (HN cells). We found that transient exposure to high glucose persistently suppressed SIRT1 expression and its deacetylase activity, while it continuously increased the expression of acetyl-p300 (Lys1499), acetyl-p53 (Lys382), p21/waf1, as well as SA-β-gal positive staining. Treatment of HN cells with resveratrol (a selective SIRT1 activator) significantly upregulated the expression and activity of SIRT1, which subsequently inhibited p53/p21-mediated endothelial senescence through deacetylation of p53 at Lys382, resulting in less SA-β-gal positive staining. Additionally, adding L002 (a selective p300 inhibitor) to HN cells also reduced SA-β-gal positive staining by repressing p300-mediated acetylation of p53 at Lys382. Furthermore, SIRT1 overexpression or activation by resveratrol in HN cells inhibited the acetylation of p300 at Lys1499, which led to suppression on p53/p21 pathway and amelioration of senescent phenotype. Of importance, SIRT1 activation by metformin also suppressed cellular senescence in HN cells.

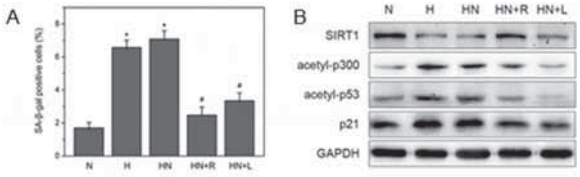

Figure. Transient hyperglycemia promoted persistent endothelial senescence. (A) the percentage of SA-β-gal possitive cells; (B) Western blot analysis. *p<0.05 vs. N; #p<0.05 vs. HN. N, normal glucose (5 mM) for 6 days; H, high glucose (30 mM) for 6 days; HN, high glucose for 1 days followed by normal glucose for 5 days; R, resveratrol; L, L002.

Taken together, our data suggested that, short-term hyperglycemic stimulation could lead to persistent cellular senescence in HUVECs via SIRT1/p300/p53/p21 pathway, and that metformin could be used in treating metabolic memory of macrovascular endothelial senescence.

4788 | BENCH
SIRT1 drives persistent myocardial dysfunction via epigenetic regulation of mitochondrial adaptor p66Shc in the diabetic heart

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Purpose: Recent evidence suggest that diabetic cardiomyopathy phenotype is not reverted by intensive treatment of hyperglycemia. The molecular mechanisms underlying persistent myocardial damage remain to be elucidated. Mitochondrial adaptor p66Shc, critically involved in reactive oxygen species (ROS) production, mediates hyperglycemia-induced cardiomyopathy. The present study investigates the role of p66Shc as determinant of persistent oxidative stress in the diabetic heart despite optimal glycemic control (OGC).
Methods: Diabetes was induced in wild-type 129sv mice (4-6 months old) by a single i.p. dose of streptozocin. Mice were divided into 5 experimental groups: 1) healthy controls; 2) untreated diabetics; 3) diabetics treated with insulin, 4) diabetics receiving insulin together with p66Shc siRNA or 5) scrambled siRNA (n=6-7/group). Insulin implants were placed subcutaneously 3 weeks after the induction of diabetes for the following 3 weeks. In vivo gene silencing of p66Shc was performed by i.v. administration of p66Shc siRNA. Measurement of superoxide anion (O2-) by ESR spectroscopy and mitochondrial swelling assay were performed in isolated cardiac mitochondria. NF-kB activity was assessed by p65 nuclear translocation and binding activity. Chromatin immunoprecipitation (ChIP) was performed to investigate the interaction between SIRT1 and p66Shc promoter. Left ventricular function was assessed by high resolution Micro-Ultrasound System (Vevo 2100, Visualsonics).
Results: O2- production and mitochondrial swelling were significantly increased in the heart of diabetic mice and OGC did not revert this phenomenon. These findings were associated with persistent upregulation of p66Shc. Moreover, expression of pro-inflammatory genes IL-6, MCP-1 and VCAM-1 was elevated in the diabetic hearts and did not change despite OGC. Consistently, left ventricular function assessed by ejection fraction (EF) and fractional shortening (FS) was impaired in diabetic mice and OGC did not restore it. Interestingly, in vivo siRNA of p66Shc at the time of glucose normalization blunted ROS production and suppressed myocardial inflammation by inhibiting NF-kB activation. Of note, p66Shc knockdown significantly improved EF and FS in comparison with insulin treatment alone. Persistent p66Shc expression was explained with reduced histone 3 deacetylation by SIRT1, leading to chromatin remodelling and continued gene transcription.
Conclusions: These findings suggest that pharmacological activation of deacetylase SIRT1 may suppress p66Shc overexpression and subsequent NF-kB activation in the setting of diabetes.

4789 | BENCH
Tumor necrosis factor receptor-associated factor (TRAF)-1 regulates myeloid cell recruitment into adipose tissue during diet-induced obesity

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Background: Accumulation of inflammatory leukocytes is a prerequisite of adipose tissue inflammation during the metabolic syndrome. We recently reported that genetic deficiency of Tumor necrosis factor receptor-associated factor (TRAF)-1 attenuates inflammatory cell recruitment in atherosclerosis. Here, we tested whether genetic deficiency of TRAF-1modulates diet-induced obesity (DIO) in mice.
Methods and results: To test the association of TRAFs and obesity we screened for expression of different TRAFs in mouse adipose tissue after 20 weeks of feeding with a high fat diet (HFD). HFD induced up-regulation of TRAF-1, -3, -5, -6, and -7 mRNA. Interestingly, the amplitude of gene regulation was highest for TRAF-1 (4.9-fold, p=0.002). To test functional relevance of our findings, WT or TRAF-1–/– mice consumed HFD for 20 weeks (n≥10 mice per group). Interestingly, TRAF-1–/– mice gained less weight during DIO (119±7.5% vs. 41±3.7% for WT and TRAF-1–/–, respectively). Accordingly, total body weight and weight of fat pads was decreased in TRAF-1–/– mice. Moreover, TRAF-1–/– mice demonstrated lowered glucose levels after intraperitoneal glucose and insulin tolerance tests. Finally, inflammatory cell recruitment was impaired in TRAF-1–/– mice with reduced numbers of adipose tissue macrophages. Functionally, circulating and splenic monocytes were lowered in TRAF-1–/– mice proposing that TRAF-1 modulates monocyte mobilization during inflammation.
Conclusion: We present the novel finding that TRAF-1 is regulated in obese adipose tissue. Genetic deficiency of TRAF-1 attenuates adipose tissue inflammation in mice by limiting monocyte recruitment. These findings identify TRAF-1 as a mediator of cardio-metabolic disease.

4790 | BENCH
A novel role for the stress hormone CRH in myocardial fatty acid metabolism

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Background: Heart depends on energy production. The body response to stressors is an adaptive systemic response mediated in great part through activation of the hypothalamic-pituitary-adrenal (HPA) axis and the release of glucocorticoid. CRH, the hypothalamic component of the HPA axis, is expressed in several tissues outside the central nervous system, including the heart. We hypothesized that CRH is critical for the basal myocardial function and/or in response to non-anticipated stressors, such as endotoxemia, and we studied its association with energy homeostasis in the heart.
Methods: The stressful/ inflammatory reaction was induced by LPS administration. Two-D targeted M-mode imaging was obtained from the short axis view at the level of greatest LV dimension. mRNA expression levels were quantified by qPCR. Histological analysis was done by H&E, Masson Trichrome, reticulin and PAS stainings, and results were assessed by specifically designed image analysis software.
Results: Crh–/– mice had significantly compromised cardiac function compared to Crh+/+ (wild-type), as determined by lower FS (%) and EF (%) values. In addition, Crh–/– exhibited histological abnormalities, including increased perivascular fibrosis and apoptosis. Expression of genes involved in fatty acid metabolism, including PPARα, PPARγ, AMPKα, ACO and Hadha was significantly reduced in Crh–/– mice. They also had lower levels of CD36, PDK4 and FAS, and of the glycolysis marker Hexokinase II; and they exhibited increased glycogen deposition compared to Crh+/+. Upon exposure to LPS, Crh–/– showed high levels of mortality (90-100% after 16-28h post-LPS), compared to no mortality among Crh+/+. Eighteen hours after LPS administration, Crh–/– had significantly reduced EF (%) and FS (%) values, greater inflammation, monocytes' infiltration, increased vas-

culature and vascular thickness, and increased levels of cardiomyocyte apoptosis compared to Crh+/+. They had increased MMPs levels, while HSPs levels failed to increase as in Crh+/+ mice. In terms of their metabolic profile, Crh–/– mice had significantly lower levels of PPARα, PPARγ, AMPKα2, PGC1β, Cpt1b, as well as ACO, ACC1 and ACC2 compared to the equivalently treated Crh+/+ mice. These results were independent of the Crh–/– mice glucocorticoid insufficiency.
Conclusion: We have shown for the first time that Crh–/– mice exhibit compromised basal cardiac function, while systemic exposure to LPS leads to defective responses, independent of glucocorticoid insufficiency. Our results indicate a novel role for CRH in cardiac function via impaired myocardium FA metabolism.

4791 | BENCH
MicroRNA-33 deficiency leads to high fat diet- induced obesity and insulin resistance in vivo

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Background: MicroRNAs (miRs) are small non-protein-coding RNAs that bind to specific mRNAs and inhibit translation or promote mRNA degradation. Recent reports, including ours, indicated that miR-33 located within the intron of sterol regulatory element binding protein (SREBP)-2 controls cholesterol homeostasis and can be a potential therapeutic target for atherosclerosis. We generated microRNA-33 deficient mice (miR-33–/–) and found that these mice showed significant increase of ABCA1 levels and serum HDL-C and resistance to atherosclerosis formation. However, unexpectedly, we noticed that miR-33–/– mice gradually gained more weight than control and the mechanisms were investigated.
Methods and results: miR-33–/– mice showed marked worsening of obesity under high fat diet (HFD: 45% fat). Computed tomography analysis showed a severe increase in body fat. Adipocyte size of miR-33–/– mice was increased with the accumulation of infiltrated cells in epididymal fat. miR-33–/– mice showed impaired glucose tolerance and insulin tolerance and increased serum insulin and leptin levels, which indicated that miR-33 deficiency showed insulin resistance under HFD. Next, we measured the metabolic rate. Oxygen consumption, activity, body temperature and urinary catecholamine levels did not differ between control and miR-33–/– mice. Food intake was slightly but significantly higher in miR-33–/– mice fed HFD, whereas this difference was not seen when fed normal chow. We searched for potential target genes of miR-33 and found that one of the targets is SREBP-1. We confirmed that miR-33 targeted the 3'UTR of SREBP-1 in vitro and the expression of SREBP-1 was increased in miR-33–/– mice. miR-33–/– mice were crossed with Srebp1+/– mice and fed HFD. The difference in body weight was decreased and abnormal glucose tolerance and serum leptin levels were ameliorated in miR-33–/– Srebp1+/– mice compared with miR-33–/– Srebp1+/+ mice.
Conclusions: These results indicated that miR-33 deficiency showed obesity and insulin resistance via up-regulation of SREBP-1 under HFD. miR-33 was also reported to target RIP140, which might contribute to these unfavorable effects, because it promotes the activity of NF-kB and regulates the expression of inflammatory genes. A careful attention for body weight gain and insulin resistance formation may be necessary when inhibition of miR-33 is applied to clinical setting, especially under over-nutrition state.

CONTEMPORARY ISSUES IN ARTERIAL HYPERTENSION

4796 | BEDSIDE
Pulse wave velocity biological behavior and characteristics in hypertensive patients: a prospective study of more than 10.000 subjects

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Objectives: Pulse wave velocity (PWV) represents an established risk factor in hypertensive patients. Increased PWV values are associated with worse outcome and PWV measurement represents a significant marker in order to assess total cardiovascular risk.
Aim and methods: This study had the purpose to assess the biological behavior and characteristics of PWV in hypertensive patients. We prospectively studied 10.103 subjects (3243 controls, 6860 hypertensive patients) from five outpatient hypertensive clinics. In all patients anthropometric characteristics as well as medical history and antihypertensive regiment was recorded. The statistical behavior of PWV was tested with respect to qualitative parameters such us gender and smoking, as well as quantitative variables such us age, BMI, systolic BP, diastolic BP and heart rate. Non parametric-test Kruskal-Wallis was utilized in order to identify the variance of PWV between control and hypertensive patients. Regression analysis was performed for all the previously mentioned parameters. Pearson's correlation test was used to asses the statistical behavior of PWV compared to the patient's baseline characteristics.
Results: PWV distribution was weighted by age due to conditionality of variance. Kruskal_wallis test revealed that PWV has a statistically significant different distribution between controls and hypertensive patients ($p<0.001$). The magnitude of PWV increase, was related to BP category classification (from optimal to stage III hypertension) ($p<0.001$). Pearson's correlation revealed a significant association of PWV practically with all major baseline characteristics of hypertensive patients (BMI, Gender, Age, Systolic BP, Diastolic BP, Smoking status and heart rate) ($p<0.001$). This association was retained after adjustment of PWV confounders. Multiple regression analysis showed that antihypertensive drug therapy does not affect the statistical significant distribution of PWV in hypertensive patients.
Conclusions: PWV is increased in hypertensive patients, the degree of PWV increase, is associated with baseline blood pressure levels (independently of the antihypertensive drug regiment used as well as anthropometric variables).

4797 | BEDSIDE
Pulse wave velocity. biological behavior and characteristics in healthy subjects: a prospective study of 3243 subjects

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Objective: Carotid femoral pulse wave velocity represents the gold standard for aortic stiffness measurement. Aortic stiffness presents an independent predictive value for fatal and non fatal cardiovascular events, and represents a significant tool for total cardiovascular risk assessment.
Aims and methods: This study had the purpose to assess the biological behavior and characteristics of PWV in healthy subjects. We prospectively studied 3243 healthy subjects from five outpatient hypertensive clinics. In all patients anthropometric characteristics as well as medical history and antihypertensive regiment was recorded. The statistical behavior of PWV was tested with respect to qualitative parameters such us Gender and Smoking, as well as quantitative variables such us Age, BMI, systolic BP, diastolic BP and heart rate. Pearson's correlation test was used to asses the statistical behavior of PWV compared to the patient's baseline characteristics. ANOVA was utilized in order to identify the distribution of PWV between differences defined by anthropometric parameters.
Results: The magnitude of PWV increase, was related to BP category classification (from optimal to high normal stage) ($p<0.001$). Pearson's correlation revealed a significant positive association of PWV practically with all major baseline characteristics of healthy subjects (BMI, Age, Gender, Systolic BP, Diastolic BP, Smoking status and heart rate) ($p<0.001$). Classification of the healthy subject with respect to their BMI revealed significant statistical changes in PWV between normal weights, overweight's and obese ($p<0.004$ and $p<0.001$ respectively).
Conclusions: PWV present a linear correlation with all major biological and anthropometirc characteristics of healthy subjects. The degree of PWV increase is associated with baseline blood pressure levels.

4798 | BEDSIDE
Resistant hypertension, patient characteristics, and risks of ischemic stroke

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Background: Little is known about the prognosis of resistant hypertension (RH) in Asian population. This study aimed to evaluate the impacts of RH in Taiwanese patients with hypertension, and to ascertain whether patient characteristics determine the outcome of RH.

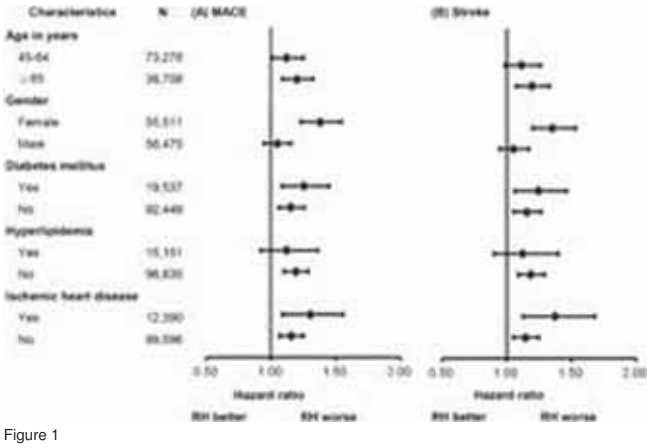

Figure 1

Methods: Patients aged ?45 years with hypertension were identified from the National Health Insurance Research Database. Medical records of 111,986 patients were reviewed in this study, and 16,402 (14.6%) patients were recognized as having RH. Risk of major adverse cardiac events (MACE) in patients with RH and non-RH was analyzed.
Results: A total of 11,856 patients experienced MACE in the follow-up period. There were more females in the RH group, they were older than the non-RH (63.1 vs. 60.5 years) patients, and had a higher prevalence of cardiovascular comorbidities. Overall, patients with RH had higher risks of MACE (adjusted HR 1.17; 95%CI 1.09-1.26; p<0.001). Significantly elevated risks of stroke (adjusted HR 1.17; 95%CI 1.08-1.27; p<0.001), especially ischemic stroke (adjusted HR 1.34; 95%CI 1.20-1.48; p<0.001), but not all-cause mortality or acute coronary syndrome were noted in patients with RH compared to those with non-RH. A propensity score matched cohort confirmed this relationship. Subgroup analysis showed that RH increased the risks of stroke in female and elderly patients. However, no significant influence was noted in young or male patients.
Conclusions: Patients with RH had higher risks of MACE and stroke, especially ischemic stroke. The risks were greater in female and elderly patients than in male or young patients.

4799 | SPOTLIGHT
What is targeted diastolic blood pressure in elderly patients? The results from the REeasons for Geographic And Racial Differences in Stroke (REGARDS) cohort study

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There are limited data on the optimal levels of diastolic blood pressure (DBP) in elderly individuals with hypertension. The aim of the study was to analyse the association of DBP and cardiovascular outcomes in elderly persons taking antihypertensive medication.
Participants with hypertension (n=13,948), enrolled in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort study were categorized into 3 age groups: 55-64, 65-74 and ≥75 years old. All groups were further divided according to baseline on-treatment DBP levels: <70, 70-79, 80-89, and >90 mmHg. Four main outcomes were analysed in the study: cardiovascular disease (CVD), coronary heart disease (CHD) and stroke incidence, and all-cause mortality rate. Median follow-up was 4.5 years for CVD and CHD, 5.7 years for stroke, and 6.0 years for all-cause mortality.
After multivariable adjustment, DBP<70 mmHg was associated with the highest risk of CVD and CHD incidence among participants aged ≥75 years, and DBP>90 mmHg with the numerically lowest CVD risk (hazard ratio [HR] 0.38, 95%CI: 0.16-0.91; p-linear=0.013, and 0.22, 95%CI: 0.07-0.69; p=0.002, respectively). No relation between DBP and CVD and CHD incidence was observed for persons aged 55-64 and 65-75 years. There was also no relation between DBP and stroke incidence for all individuals aged ≥55 years. For participants aged 55-64 years DBP<70 mmHg was associated with the highest risk of all-cause mortality (p-linear=0.009). The J-curve relation was observed in this group, with the increased risk of death also for DBP>90 mmHg (p-quadratic=0.01). The same relation was noticed for subjects ≥75 years (p-quadratic=0.022), however with the highest risk for DBP>90 mmHg (1.54, 95%CI: 1.11–2.13). Among participants aged 65-74 years, there was a linear relation between DBP and all-cause mortality with the highest risk for DBP <70 mmHg (p=0.039).
The results suggest a hypothesis that for all individuals ≥55 the recommended level of DBP should be between 70 and 90 mmHg, with the special caution for DBP<70 mmHg. This finding needs to be tested in a future randomized controlled trial.

4800 | BEDSIDE
Masked hypertension in midlife women: prevalence, risk factors intensity, state of target organs

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Objective: To determine the prevalence of masked hypertension (MHT), to assess risk factors intensity and target organs state in midlife women in screening. Design and methods: We evaluated 784 women (employees of industrial institution), 40 to 60 yrs old, with initial blood pressure (BP) <140 and 90 mm Hg with no clinical signs and anamnesis of arterial hypertension (AH) or any evidence of cardiovascular disease (CVD). MHT was diagnosed by 30-s breathhold test (BH test) conducted when excluding any environmental influences on the test findings. Sitting BP was measured initially and remeasured after 30 seconds of breath holding. BH test was considered to be positive when systolic BP increased >140 mm Hg and diastolic increased >90 mm Hg. After 2 days in all patients with positive BH test results 24-h ambulatory BP monitoring (ABPM), physical examination and assessment of CVD risk factors intensity were performed.
Results: BH test was positive in 8.5%patients (67). In all 67 patients data of 24-h ABPM showed threshold exceeding of averaged BP, load indices of BP overtoped 50%. These findings confirm the presence of AH, educed by provocative strain – BH test. During physical examination diastolic dysfunction of the left ventricle was present in 71.6% (48) of women, retinal angiopathy - in 47.7% (32). All 67 patients with positive BH test results had albuminuria. The majority of patients - 73.1% (49 women) had ≥2 CVD risk factors of various intensity.
Conclusions: Masked hypertension was diagnosed in 8.5% of midlife women. The presence of masked hypertension was accompanied by target lesions, manifesting with albuminuria, diastolic dysfunction of the left ventricular, retinal angiopathy; and by ≥2 risk factors, that point at underdiagnosis of MHT and lack of forehanded care.

4801 | BEDSIDE
Arterial hypertension after successful aortic decoarctation: atenolol vs enalapril

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Background: Late arterial hypertension, a very frequent complication in aortic coarctation (AoC) patients after repair, has been identified as a major predictor for morbidity and mortality in AoC patients. Although the most used in the clinical practice, there is very few data about efficacy and tolerability of ace-inhibitors vs. beta blockers in young AoC patients.
Aim: To evaluate the tolerability and efficacy (24h blood pressure and left ventricular mass [LVMI]), of oral administration of atenolol vs enalapril.
Methods: We enrolled consecutive AoC hypertensive patients with a) no history of blood pressure treatment or after >48h of withdrawn, b) aged 6-20 years, c) BMI <90° pc for age-and-sex, d) >12 months from AoC repair, e) no major associated cardiovascular abnormalities, and f) isthmic gradient <20 mmHg. All patient were evaluated with 24h-ambulatory blood pressure monitoring, standard echocardiography, strain-strain rate imaging, at enrolment, 3, 6, and 12 months of treatment.
Results: We studied 51 AoC patients (12.5±3 years, BMI: 22.9±4.2kg/m^2). Patients were randomly assigned at Atenolol treatment (Group I, n=26) (0.5–2 mg/kg), or Enalapril treatment (Group II, n=25) (0.08–0.6mg/kg). Of them, 42 completed the study, 5 patients had a 6 month follow-up and 4 patients 3 month follow-up.
Efficacy: Both drugs were able to significantly reduce 24-systolic blood pressure (Group I: 132.6±12 vs. 124±16mmHg, p=0.02; Group II: 134.6±5.8 vs. 130±7mmHg, p=0.03), however only enalapril was able to significantly reduce LVMI (47±12 vs. 39.6±10g/height$^{2.7}$, p=0.01). No changes were induced by the treatment on left ventricular systolic and diastolic function or on isthmic gradient. Also myocardial deformation studied parameters did not change significantly during treatment.
Tolerability: Group I: in two cases (7.7%) drug withdrawal was needed because of side effects. Group II: in no cases drug withdrawal was needed (p=0.49).
Conclusions: Our study demonstrated for the first time in AoC young patients that: 1. Enalapril and Atenolol are similarly effective in reducing 24h systolic blood pressure. 2. Only Enalapril demonstrated a significant reduction of LVMI. 3. Enalapril and Atenolol do not influence the isthmic gradient. 4. Enalapril does not present side effects in our studied sample.

NEW STRATEGIES TO REDUCE PERCUTANEOUS CORONARY INTERVENTION COMMUNICATIONS

4819 | BEDSIDE
How to choose the best antispastic agent to prevent radial artery spasm during percutaneous coronary interventions?

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Background: Radial artery spasm (RAS) is and remains one of the major limitations for transradial approach, especially among transfemoralists physicians. Our team has performed previously three successive randomized controlled trials sharing the same methodology and endpoints and evaluating different vasodilator agents in the prevention of RAS. We are reporting the results of the pooled analysis of our three studies.
Methods: A total of 1950 patients were consecutively randomized to receive diltiazem, verapamil, molsidomine, isosorbide dinitrate (ISDN) or placebo, through the arterial sheath after radial artery catheterization. The primary endpoint was the occurrence of a RAS defined as a limitation of the catheter movement and/or a significant pain perceived by the patient during catheter mobilization. Secondary endpoints included the occurrence of symptomatic or significant fall of systolic blood pressure and determination of independent predictors of RAS.

Univariate and multivariate odds ratios of radial spasm

	Univariate			Multivariate*		
	OR	95% CI	P	OR	95% CI	P
Placebo	1			1		
Molsidomine	0.54	0.32–0.91	0.02	0.51	0.30–0.88	0.015
Verapamil 2.5	0.44	0.29–0.67	0	0.43	0.28–0.66	0
Verapamil 5	0.3	0.16–0.55	0	0.28	0.15–0.52	<0.0001
Verapamil 2.5 + molsidomine	0.18	0.09–0.36	<0.0001	0.16	0.08–0.34	<0.0001
Risordan	0.73	0.45–1.17	0.19	0.75	0.45–1.23	0.28
Tildiem	1.27	0.82–1.96	0.29	1.24	0.78–1.97	0.35

OR were estimated by logistic regression. *Analysis was adjusted for age, sex, number of catheters and sheath size.

Results: RAS occurred in 44/198 patients (22.22%) in the placebo group with a significant reduction in the molsidomine 27/203 (13.3%) and verapamil 88/847 (10.4%) groups (P=0.02). The rate of occurrence of RAS was similar between the placebo, ISDN and diltiazem groups (P=0.2).
Conclusion: Among vasodilator agents, verapamil and/or molsidomine showed the best efficacy to prevent RAS without affecting patient safety. Their use reduces the occurrence of RAS more than 50%. ISDN and diltiazem should be avoided as they don't prevent RAS.

4820 | BEDSIDE
Periprocedural stroke is not independently affected by the access site during coronary angiography and PCI

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Introduction: All coronary angiography (CA) and percutaneous coronary intervention (PCI) performed in Sweden, including any periprocedural complications, are reported to the Swedish Angiography and Angioplastic Registry (SCAAR).
Aim: To see if the incidence of periprocedural stroke during CA and PCI differs between the radial and the femoral access.
Methods: All CA and PCI procedures and all neurological complications registered in SCAAR between 2003 and 2010 were analyzed. Two neurologists evaluated all the periprocedural neurological complications. To identify true periprocedural stroke the SCAAR data was cross-checked with the patients medical records.
Results: A total of 259 045 CA and PCI procedures were compiled, of these 30 804 were excluded due to unknown vascular access site. Of 662 reported neurological complications 12 were unverifiable and thus excluded. Finally 227 833 procedures without neurological complication and 408 stroke verified to be true periprocedural complications were analyzed.
The radial access, used in 34% of the 228 241 procedures, had a significantly lower incidence of periprocedural stroke. After adjusted logistic regression analyses the access site was found not to be an independent risk factor.

Patient characteristics and results

Variable	Femoral (N=151,086)	Radial (N=77,155)	p value
Age (mean ± SD)	66±11	65±11	***
Female gender (%)	34.9	33	***
Diabetes mellitus (%)	17.2	16.5	***
Previous CABG (%)	9	2.9	***
Previous stroke (%)	6.6	5.5	***
Angiographic findings (%)			***
normal	27.6	34.6	
1-VD	25.9	27.4	
2-VD	18.5	17.7	
3-VD	27.9	20.3	
Neurological complications (%)	0.2	0.1	*
Logistic regression analyses Radial versus femoral access	Odds ratio	Confidence interval	p value
Multivariate model †	0.94	(0.75–1.17)	0.55

CABG, coronary artery bypass graft; 1-2-3-VD, 1-2-3 vessel disease. *p<0.05, ***p<0.001, †Multivariate model adjusted: including age, gender, previous CABG, previous stroke, diabetes mellitus, vascular access site.

Conclusion: The incidence of periprocedural stroke during CA and PCI differed between the access sites. The risk of periprocedural stroke was not dependent on the access site, instead on the degree of cardiovascular disease.

4821 | BEDSIDE
Fate of patients with coronary perforation complicating PCI: insights from the Euro Heart Survey PCI registry

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Background: Coronary perforation (CP) is a life-threatening complication during percutaneous coronary intervention (PCI). However, little is known about the incidence and the clinical outcome of CP in modern high-volume interventional centers.
Methods: Between 2005 and 2008 a total of 47,407 consecutive patients undergoing PCI were prospectively enrolled into the PCI-Registry of the Euro Heart Survey Programme. For the present analysis patients with CP (n=124, 0.3%) were compared to those with no CP (n=41,944, 99.7%)
Results: Patients suffering from CP were older, more often female, had more severe coronary disease and underwent more complex coronary interventions (table). More than 10% of the patients developed a tamponade. In only a small minority an emergency CABG had to be performed. In-hospital mortality was markedly elevated in patients with CP.

	Perforation	No perforation
Age	66.2±11.3	63.5±11.3
Female	34.7%	25.8%
PAD	12.2%	5.9%
ACS	59.7%	51.2%
3-vessel disease	29.5%	20.8%
Type C lesion	53.2%	24.0%
Rotablation	2.5%	0.2%
Acute segment closure	6.6%	0.5%
Tamponade	11.3%	0.0%
Acute cardiac arrest	3.6%	0.5%
Emergency CABG	3.3%	0.1%
Hospital death	7.3%	1.5%

Conclusions: In this real-world registry the incidence of CP was quite low. CP occurred more often in patients with complex coronary interventions and was associated with a fourfold increase of hospital mortality.

4822 | BEDSIDE
Comparison of low dose versus standard dose heparin for radial approach in elective coronary angiography?

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Objective: The aim of this study is to evaluate the efficacy and safety of two doses of heparin, a low dose (2500 IU) and a standard dose (5000 IU) in patients who underwent trans-radial coronary angiography (TRCAG).
Methods: A total of 459 consecutive patients were included in the present study, 217 in the 2500 -IU heparin group and 242 in the 5000-IU heparin group. Radial artery patency was evaluated one month after the TRCAG with Doppler ultrasonography.
Results: The radial artery occlusion (RAO) was observed in 15 (3.3%) patients. The RAO was significantly higher in 2500 IU heparin group than 5000 IU heparin group (5.5% vs 1.2% p=0.010, respectively). Female gender (Odds ratio (OR)= 66.135, p=0.002, 95% confidence interval (CI) =4.584-954.131), presence of hypertension (OR= 0.022, p=0.005, 95% CI = 0.002-0.307), sheath removal time (OR= 1.496, p<0.001, 95% CI =1.254-1.784) and administration of 2500 IU heparin (OR= 9.758, p=0.034, 95% CI =1.195-79.695) were the independent predictors of RAO in multivariate regression analysis.

Table 1. Patient characteristics

Variable	2500 IU Heparin (n=217)	5000 IU Heparin (n=242)	p
Male, n%	160 (73.7%)	195 (80.6%)	0.080
Age, year	58.85±9.82	60.72±10.63	0.052
Body mass index, kg/m^2	27.35±4.24	27.65±4.19	0.445
Hypertension, n%	119 (54.8%)	126 (52.1%)	0.552
Dyslipidemia, n%	121 (55.8%)	156 (64.5%)	0.057
Diabetes Mellitus, n%	40 (18.4%)	54 (22.3%)	0.304
Glomerular filtration rate, ml/min	90.4 (30.7)	90.3 (34.5)	0.982
Fluoroscopy time, sc	150 (79.5)	142.5 (75.3)	0.065
Procedure time, min	7 (2)	6.5 (2)	0.391
Sheath removal time, min	12 (5)	12 (7)	0.732
Hematoma, n%	0	5 (2.1%)	0.063
Radial artery occlusion, n%	12 (5.5%)	3 (1.2%)	0.010

Conclusion: The patients in the standard dose heparin group has lower RAO rates compared to low dose group in this study. This suggests that using the current technique, standard dose of heparin is still required for transradial diagnostic angiography.

4823 | BEDSIDE
Statins for the prevention of contrast-induced nephropathy: a meta-analysis of randomized controlled trials and observational studies

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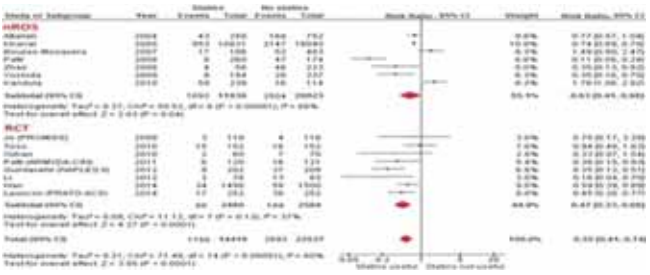
Purpose: Studies focusing on statin therapy to prevent contrast-induced

nephropathy (CIN) have shown conflicting results. We aimed at assessing the impact of statin treatment on the incidence of CIN after coronary angiography in a meta-analysis of published trials.
Methods: We systematically searched the PubMed database for studies published in 1970-2014 and examining the association between statin therapy and the incidence of CIN. Search strategy included "statin AND contrast-induced nephropathy OR statin AND contrast OR statin AND contrast media"; "statin AND catheterization OR statin AND angiography". Mantel-Haenszel pooled estimates of Risk Ratio (RR) and 95% confidence intervals (CI) for CIN incidence were assessed using random effects models.
Results: We identified a total of 15 studies: 8 randomized controlled trials involved 4,984 statin-naïve patients and 7 non randomized studies included 31,959 patients. The use of statins before angiography was associated with a significant relative risk reduction of CIN (RR 0.55; 95% CI 0.41-0.74). When analyzed according to the study design, pooled estimates of RR (and associated 95% CI) for CIN were 0.47 (0.33-0.66) for randomized trials and 0.63 (0.41-0.98) for observational studies. A funnel plot showed no evidence of publication bias.



Forest plot. Outcome: CIN incidence.

Conclusions: Our meta-analysis suggests that statin therapy is associated with a significant reduction in the incidence of CIN in patients undergoing coronary angiography.

4824 | BEDSIDE
Association of bleeding avoidance strategies with bleeding and in-Hospital mortality in men and women undergoing percutaneous coronary intervention

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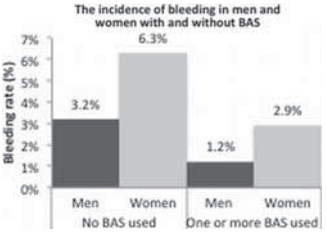
Purpose: The use of any of the bleeding avoidance strategies (BAS) (radial access, bivalirudin and/or vascular closure devices) has been shown to be associated with lower bleeding among men and women undergoing percutaneous coronary intervention (PCI). However, the relationship of BAS with sex-related mortality in PCI patients is unknown.
Methods: We examined the relationship of BAS with sex-related bleeding and in-hospital mortality among 96,693 patients undergoing PCI enrolled in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2) (2010-2012).
Results: BAS were utilized similarly in men and women undergoing PCI (69.2 vs. 68.9%). For both men and women, in patients where any BAS was utilized the incidence of bleeding events was less than 50% of that observed for patients in whom none of the strategies were employed (Figure). Compared to those without the use of BAS, utilization of this strategy was associated with lower risk of observed mortality in men (0.6 vs. 2.6%, $p<0.05$) and in women (1.0 vs. 3.7%, $p<0.05$).



Conclusions: Our data confirmed that any BAS was associated with lower observed bleeding rates in both sexes undergoing PCI. This lower bleeding risk was associated with lower risk of observed mortality in both men and women. Future prospective studies are needed to evaluate the role of BAS in reducing post-PCI bleeding and mortality.

BIOMARKERS IN HEART FAILURE. NEW INSIGHTS

4829 | BEDSIDE
Direct comparison of B-type natriuretic peptide and midregional pro-atrial natriuretic peptide in the diagnosis of acute heart failure

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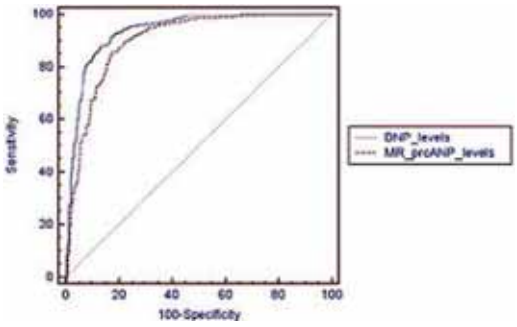
Purpose: The concentration of atrial natriuretic peptide (ANP) in the circulation is 10-50 fold higher compared to B-type natriuretic peptide (BNP). Pilot studies have suggested that midregional pro-atrial natriuretic peptide (MR-proANP) might have similar accuracy as BNP in the diagnosis of acute heart failure (AHF). We aimed to validate this finding.
Methods: We enrolled 1111 unselected patients presented with acute dyspnea to the emergency department (ED). Levels of MR-proANP were measured at presentation in a blinded fashion. The final diagnosis (AHF or other causes of acute dyspnea) was adjudicated by two independent cardiologists using all information pertaining to the individual patient including ECG, chest x-ray, echocardiography, and levels of BNP.
Results: AHF was diagnosed in 740 patients (66%). The median values of both MR-proANP and BNP were significantly higher in patients diagnosed with AHF. Overall, the correlation of levels of MR-proANP with that of BNP was high ($r=0.73$; $p<0.001$). Quantifying diagnostic accuracy for AHF by the area under the receiver operating characteristics curve (AUC) revealed 0.936 (95%CI, 0.919 to 0.949) for BNP, and 0.898 (95% CI, 0.879 to 0.916) for MR-proANP ($p<0.001$ for the comparison). Combining MR-proANP and BNP using logistic regression resulted in an AUC for the diagnosis of AHF of 0.936 (95% CI, 0.919-0.952), which was similar to that of BNP alone ($p=0.99$). In none of the pre-defined subgroups MR-proANP appeared to be superior to BNP.



ROC for MR-proANP and BNP

Conclusion: MRproANP and BNP both have a very high accuracy for the diagnosis of AHF. In the overall population, we were unable to demonstrate added diagnostic value of MR-proANP on top of BNP. The slightly higher accuracy of BNP may at least partly be explained by the study design.

4830 | BEDSIDE
Combined measurements of N-Terminal Pro-Brain Natriuretic Peptide and D-Dimer are useful when predicting in-hospital death in acute heart failure

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Aims: NT-proBNP is an established biomarker for the prediction of in-hospital death in patients with acute heart failure. We therefore hypothesized that a combined approach using both NT-proBNP and D-dimer levels might improve the clinical risk stratification for heart failure.
Methods: In total, 287 patients presented to our emergency room within 24 h of symptom onset were included, and NT-proBNP and D-dimer levels were simultaneously measured. The optimal cut-off level for NT-proBNP and D-dimer to predict in-hospital death was determined by receiver operating characteristics curve anal-

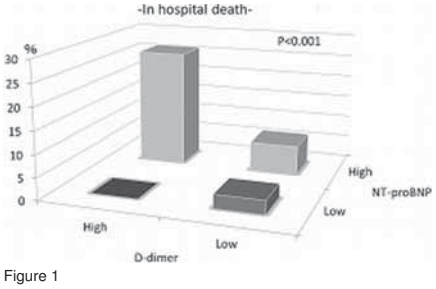

Figure 1

ysis. The integrated prognostic impact of NT-proBNP and D-dimer levels above each cut-off value was also examined.
Results: In-hospital death occurred with 20 patients (7.0%). The optimal cut-off levels for NT-proBNP and D-dimer were 4900 pg/mL and 4.0 mg/dL, respectively, with corresponding odds ratios (OR) of 5.32 (p=0.001) and 3.54 (p=0.005). Patients presenting with higher cut-off levels of both NT-proBNP and D-dimer exhibited the highest risk for in-hospital death compared with the other patients (24.4% vs. 4.1%; OR = 7.65, p<0.001). Multivariable analysis indicated that the integrated biomarkers remained independent predictors of in-hospital death (OR = 11.20, p=0.002).
Conclusion: The combination test with both the NT-proBNP and D-dimer biomarkers was useful for the prediction of death in patients with acute heart failure.

4831 | BEDSIDE
Activation pattern of novel renal biomarkers in acute heart failure: superiority of NGAL

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Background: Patients with acutely decompensated heart failure often suffer from deterioration in renal function, also referred to as cardiorenal syndrome (CRS). The aim was to assess and compare a set of novel markers of acute kidney injury (AKI) in acute heart failure (AHF).
Methods: The new renal biomarkers Neutrophil Gelatinase-Associated Lipocalin (NGAL), Kidney injury molecule-1 (KIM-1), N-acteyl-ß-D-glucosaminidase (NAG) and Interleukin-18 (Il-18) were assessed from urine samples of 58 patients with AHF and 54 healthy controls.
Results: Upon admission, NGAL, KIM-1 and NAG, but not Il-18 (p=n.s.), were significantly elevated in patients with AHF as compared to healthy controls (each p<0.05). The novel renal markers were neither significantly correlated with established renal parameters like serum creatinine, cystatin C and eGFR nor with proteinuria markers (urinary protein, albumin). Among all 58 patients, 23 (39.7%) patients developed acute kidney injury, as defined by increase of serum creatinine >0.3 mg/dL. At all sampling points, only NGAL was significantly higher in AKI patients than in patients without AKI (each p<0.05), whereas KIM-1, NAG and Il-18 did not differ (all p= n.s.). NGAL at day 2 predicted significantly developing AKI in a logistic regression analysis, beside age and eGFR (each p<0.01). Upon ROC analysis, NGAL allowed to predict AKI with a sensitivity of 78% and specificity of 52% (AUC 0.73). There was no association between NGAL and cumulative diuretic dosis, length of i.v. diuretic therapy or hospital stay.
Conclusions: NGAL, KIM-1 and NAG, but not Il-18, are elevated in patients with acute heart failure. This finding is independent from eGFR and serum creatinine and indicates tubular injury in acute heart failure. Among these novel renal biomarkers, NGAL performs moderately but superior to other novel renal biomarkers to detect acute kidney injury in acute heart failure.

4832 | BEDSIDE
Prognostic value of autoantibodies against cardiac troponin I and myosin in peripartum cardiomyopathy: a case-control study

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Background: Peripartum cardiomyopathy (PPCM) is a major cause of pregnancy-related maternal heart failure typically developing towards the end of pregnancy or in the months following delivery. Autoimmune responses in the pathogenesis of PPCM have been proposed upon identification of autoantibodies (AABs) to cardiac antigens in small retrospective case series. However, an abnormal humoral immunity in PPCM has not been established. In the present study, we evaluated circulating AABs against cardiac myosin and Troponin I (TrI) in the sera of PPCM patients with regard to clinical presentation and outcome.
Results: We investigated 59 PPCM patients with a mean left ventricular ejection fraction (LVEF) of 28±10% at time of diagnosis and 18 healthy postpartal women (LVEF >55%). 42% of the PPCM patients were tested positive for AABs, which was significantly higher as compared to healthy postpartal women (11%). Patients who were positive for one or both ABB had a significantly lower LVEF at first admission (AABneg 23.6±1.4% vs AABpos 21.2±1.6%, p<0.0001). This was observed for both types of AABs, for anti-myosin (18.9±1.9%, p<0.0001 vs AABneg) and anti-TrI (23.3±2.5%, p<0,005 vs AABneg). The baseline NTproBNP values were higher in AAB positive patients (AABneg 3556±674 pmol/l vs AABpos 8047±1595 pmol/l, p<0.01) with similar results for anti-TrI (7681±2169 pmo/l, p=0.02 vs ABBneg) and anti-myosin (8721±1900 pmol/l, p=0.002 vs ABBneg) reflecting the severity of heart failure at the acute presentation. Pericardial effusion was observed twice as frequently in AAB positive patients (ABBneg 41% vs ABBpos 85%). The mean follow-up LVEF of all patients after 6±3 months increased from 28±10% to 48±13%. Of AABneg patients 100% displayed significant improvement (+10%LVEF and change by 1 NYHA class) and 71% showed full cardiac recovery (LVEF ≥55%). In contrast, only 88% of AABpos patients displayed improved LVEF at follow-up with a full recovery rate of only 14%. Notably, none of the patients with anti-TrI AABs showed full cardiac recovery during follow-up. Two of the AABpos patients needed a left ventricular assist device and one patient received heart transplantation.
Conclusion: The results of this study suggest that anti-TrI and anti-myosin AABs may be useful biomarkers for stratification of the prognosis and to predict responsiveness to treatment in PPCM patients. Further studies are required to clarify cellular and molecular circuits leading to elevated levels of AABs and their pathophysiological relevance for disease initiation and progression in PPCM.

4833 | BENCH
Correlates and prognostic implications of dipeptidyl peptidase IV levels in patients with chronic heart failure

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Purpose: Dipeptidyl peptidase IV (DPPIV) is a serine protease that inactivates various peptide hormones including B-type natriuretic peptide (BNP) and glucagon-like-peptide 1 (GLP-1), an incretin involved in glucose homeostasis. DPPIV is a target of glucose-lowering drugs gliptins and may be involved in pathophysiology of heart failure (HF). We investigated biochemical correlates of DPPIV and its impact on HF prognosis.
Methods: Patients with advanced HF, referred for pre-transplant evaluation or ICD/CRT implantation, underwent fasting blood sampling, echocardiography and were prospectively followed for combined endpoint of death, LVAD or heart transplantation. DPPIV was measured by ELISA (DPPIV/CD36, R&D, USA), BNP by CMIA (Abbott, USA).
Results: 369 subjects (mean age 59±11 years, 84% males, BMI 28±4.7 kg/m^2, DM in 34%) with advanced HF (NYHA≥III in 72%, 54% due to CAD) were examined. DPP IV levels followed normal distribution with mean 351±92 pg/ml. DPPIV level was unrelated to log BNP (Figure 1A), to severity or etiology of HF (NYHA class, MLHFQ score, p>0.05), to degree of cardiac dysfunction (LV EF, LV diameter, both p>0.05), to BMI, gender or DM. DPPVI correlated with glucose (r=0.23, p<0.001) and HgbA1C (1B), but not with fasting insulin (r=0.04, p=0.4) or HOMA index of insulin resistance (p=0.07). DPPIV correlated with ALP (r=0.30, p<0.001) and GGT (r=0.34, p<0.001), but not with ALT and AST or IVC diameter. After median follow-up of 536 (IQR254-850) days, 36% subjects experienced adverse event. There was no difference in event-free survival by DPPIV terciles (1C).

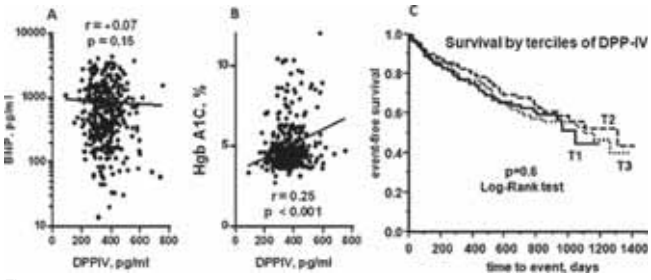

Figure 1

Conclusions: DPPIV is not related to total BNP, degree of HF or prognosis. Elevated DPP-IV is associated with impaired glucose tolerance in HF, independently of insulin resistance, and may be related to liver steatosis.

4834 | BEDSIDE
Diagnostic and prognostic performance of multiple biomarkers for acute heart failure in older patients presenting to the emergency department

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Background: The management of acute heart failure (AHF) in older patients is associated with some diagnostic challenges, which are not adequately considered in current ESC guidelines. An approach to diagnosis and prognosis is to measure N-terminal pro-B-type natriuretic peptide (NT-proBNP). But the threshold for NT-proBNP increases not only with age often due to an impaired renal function, but also differs for patients presenting with acute onset or worsening of symptoms to an emergency department (ED) and those presenting with a more gradual onset of symptoms. Thus, emergency physicians involved in the management of older AHF patients daily encounter the diagnostic and prognostic limitations of NT-proBNP. In this setting, the use of additional biomarkers may be helpful for a fast diagnostic and prognostic work-up. We prospectively investigated the di-

agnostic and prognostic performance of NT-proBNP alone or in combination with other biomarkers for AHF in older patients presenting to the ED.
Methods: We consecutively enrolled 302 non-surgical patients ≥70 years presenting to the ED. In addition to NT-proBNP, mid-regional pro-adrenomedullin (MR-proADM), mid-regional pro-atrial natriuretic peptide (MR-proANP), C-terminal pro-endothelin-1 (CT-proET-1) and ultra-sensitive C-terminal pro-vasopressin (Copeptin-us) were measured at admission. Two cardiologists independently adjudicated the final diagnosis of AHF after reviewing all available baseline data excluding the biomarkers. All patients were followed up for cardiovascular-related death within the following 12 months.
Results: AHF was diagnosed in 120 (40%) patients (age 81±6 years). Accuracy to diagnose AHF was significantly higher for MR-proADM and NT-proBNP versus NT-proBNP (area under the receiver operating characteristic curve [AUC] 0.84 versus 0.81, P=0.045) and for CT-proET-1 and NT-proBNP versus NT-proBNP (AUC 0.86 versus 0.81, P=0.031). No other dual or triple biomarker combination showed higher and significant AUC values than MRproADM or CT-proET-1 combined with NT-proBNP. When added to NT-proBNP, a continuous net reclassification improvement of 33.3% for MR-proADM and 69.9% for CT-proET-1 could result in significant reclassification of older patients. Cox regression analysis revealed a 1.99-fold risk of death (95% CI 1.61 to 2.45, P<0.001) for an increment of the log-transformed MR-proADM concentration by 1 unit after adjustment for risk factors.
Conclusions: In unselected older patients presenting to the ED, CT-proET-1 or MR-proADM and NT-proBNP improve the diagnostic and MR-proADM the prognostic performance in AHF.

ORAL ANTICOAGULATION IN PRACTICE

4843 | BEDSIDE
Effect of smoking on comparative efficacy of antithrombotic therapy in patients with atrial fibrillation. A community based cohort study

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Smoking is incorporated in a simple score (SAMe-TT2R2) that can predict poor INR control in patients with atrial fibrillation (AF) treated with vitamin K antagonists (VKA). Moreover, the clinical benefit of clopidogrel in reducing myocardial infarction and stroke in randomized clinical trials of antiplatelet drugs (APD) was seen primarily in smokers, with little benefit in nonsmokers. We made the hypothesis that active smoking may differently influence 1) the risk of stroke and 2) the risk of bleeding in AF patients treated with VKA or with APD.
Methods: We examined the clinical course of 7.948 consecutive patients with AF and/or atrial flutter seen between 2000-2010. The outcomes in patients with active smoking were compared with those in other patients.
Results: Among 7.948 patients with AF (age 71±15 years), 1034 (13%) had active smoking. APD was prescribed on an individual basis for 2761 patients (35%) and VKA for 4534 (57%). During a follow-up of 929±1082 days, 631 strokes/thromboembolic events, 707 severe bleedings and 248 major BARC bleedings were recorded. Smoking was not independently associated with a higher risk of stroke in these AF patients (relative risk=0.94, 95% CI 0.75-1.18, p=0.62). By contrast, after adjustment on age, CHADS2 score, HASBLED bleeding risk score, VKA use and APD use, smoking was independently associated with a worse prognosis for the risk of severe bleeding (relative risk=1.23, 95% CI 1,02-1,50, p=0.03) and for the risk of major BARC bleeding (relative risk=1.40, 95% CI 1.03-1.91, p=0.03). Smoking was independently associated with a higher risk of bleeding in patients treated with VKA (relative risk= 1.32, 95% CI 1.04-1.66. p=0.02) whilst this association did not reach significance in patients treated with APD (relative risk=1.31, 95% CI 0.97-1.76. p=0.07).
Conclusions: In AF, there was a higher risk of bleeding in smokers, mainly in those treated with VKA.

4844 | BENCH
Dabigatran-induced anticoagulant and bleeding effects can be reversed with both prothrombin complex concentrates and a specific antidote (idarucizumab) in a lethal porcine polytrauma model

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Introduction: A specific reversal agent in situations of life-threatening bleeding with the direct thrombin inhibitor dabigatran is currently not available and methods used in the clinic to reverse its effects have demonstrated conflicting results. This study assessed the ability of a four-factor prothrombin complex concentrate (PCC) and a specific antidote to dabigatran (idarucizumab) to reverse dabigatran anticoagulation in a porcine polytrauma model.
Methods: After ethical approval, the study was performed in 24 anaesthetised male pigs. Dabigatran was given orally for 3 days (30 mg/kg bid) and, on the 4th day, infused prior to blunt liver injury and bilateral femur fractures. Following hemorrhagic shock, blood loss (BL) was recorded 10 min post-trauma and animals were randomized (n=6/group) to a single injection of PCC (25 and 50 IU/kg), the antidote idarucizumab (60 mg/kg) or vehicle (control). BL and hemodynamic variables were monitored over 300 min or until time of death. Coagulation was assessed by thromboelastometry, coagulation parameters and diluted TT. Data were analysed by ANOVA (± SD).
Results: Dabigatran levels were 550±155 ng/mL prior to injury. Except for idarucizumab treated animals, plasma levels remained significantly elevated in all animals throughout the observation period. The degree of injury was similar among animals 10 min post injury with comparable BL of 742±133 mL. Anticoagulation with dabigatran without intervention resulted in a BL of 3774±628 mL and mean survival time of 106 min (range: 65 -146 min; p<0.05 vs PCC and idarucizumab treated animals). In contrast, treatment with 50 IU/kg PCC (1767±135 mL) and idarucizumab (1109±167 mL) was associated with a significant reduction in BL (p<0.05 vs. controls) and 100% survival. Although the onset of bleeding was reduced in PCC 25 animals, the total BL was comparable to control animals. Likewise, coagulation parameters improved substantially in PCC 50 IU/kg and idarucizumab treated animals. Due to on going blood loss, coagulopathy in control and PCC 25 animals aggravated over time. Clinically and macroscopically no adverse events were observed with idarucizumab or PCC treated animals.
Conclusion: This polytrauma model in pigs shows that therapy with aDabi-Fab is effective and safe to reverse dabigatran anticoagulation under conditions of life-threatening bleeding resulting from severe trauma. However, until idarucizumab becomes available clinically, our data also show that PCCs at sufficiently high concentrations may be an alternative to stop trauma- and dabigatran induced bleeding.

4845 | BEDSIDE
Safety of new oral anti-coagulants versus conventional agents with respect to clinically significant bleeding risk: a systematic review and networking meta-analysis of randomized controlled trials

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Background: New oral anticoagulants (NOACs) are well established as convenient and safe alternatives to conventional agents (Vitamin K antagonists) across a range of clinical conditions. Bleeding in the absence of a specific antidote is a potential complication associated with NOACs as compared to warfarin. In the absence of head to head comparisons of relative safety profiles, the choice of a specific NOAC is challenging. This study seeks to compare bleeding risks among the different NOACs using a networking meta-analysis.
Methods: Literature search was conducted using Medline, Embase, Cochrane Central Register of Controlled Clinical Trials and Cochrane Database of Systematic Review (CDSR) from the inception of these databases till the present (August 2013). We included clinical trials reporting the bleeding risk associated with the use of NOACs compared with placebos or conventional agents (low molecular weight heparins, aspirin and warfarin). Networking meta-analyses using both fixed and random effects were performed using WINBUGS 14. Subgroup analyses were performed for acute coronary syndrome (ACS), atrial fibrillation (AF), and prevention of venous thromboembolism (VTE) after orthopedic surgery. NOACs were ranked based on their likelihood to cause bleeding using a random effects model.
Results: A total of 673 titles were retrieved and 42 clinical trials (166,889 patients, 92727 in the NOAC's group and 74162 in the control group) were included in the final analyses. Results from our networking meta-analysis suggested that overall, apixaban (OR=0.77, 95% CI= 0.69-0.88) and dabigatran (OR=0.87, 95% CI= 0.78-0.97) cause significantly less bleeding compared with rivaroxaban which was associated with a significantly increased (OR= 1.12, 95% CI= 1.04-1.20) bleeding risk. In subgroup analyses rankograms showed that apixaban was associated with the least number of bleeding events followed by dabigatran and rivaroxaban in ACS and AF, whereas rivaroxaban was associated with the least bleeding events followed by apixaban and dabigatran in prevention of VTE.
Conclusions: There are clinically important differences in the bleeding risk of NOAC's among the commonly prescribed NOACs. In the absence of head to head trials, indirect evidence provides useful information for clinicians to guide the prescription of NOACs for specific clinical conditions. An important limitation of this analysis is that the patient populations studied with the various NOACs differed significantly in their composition.

4846 | SPOTLIGHT
Novel oral anticoagulants in patients with venous thromboembolism and active cancer: a systematic review and meta-analysis

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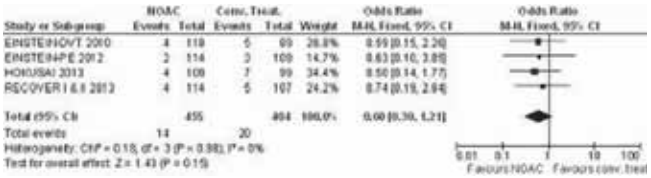
Purpose: Novel oral anticoagulants (NOACs) have been shown to be as effective as conventional anticoagulation for the prevention of recurrences in patients with venous thromboembolism (VTE). Whether this is the case in patients with cancer associated thrombosis remains undefined.

Methods: We performed a meta-analysis of randomized controlled trials with the aim of assessing the efficacy and safety of NOACs in patients with VTE and active cancer. MEDLINE, EMBASE and CENTRAL were searched up to December 2013 with no language restriction. The primary outcome of the analysis was recurrent VTE. Data on VTE recurrence and major or clinically relevant non major bleeding (CRB) were collected. Data were pooled and compared by ORs and 95% CIs.
Results: Overall, 10 studies comparing NOACs with conventional anticoagulation for treatment of VTE and reporting on outcomes in patients with active cancer were included in the review. Five studies were included in the meta-analysis (2 with dabigatran, 2 rivaroxaban and 1 edoxaban), accounting for a total of 859 patients. VTE recurrence occurred in 14 of 455 (3.1%) and in 20 of 404 (4.9%) cancer patients treated with NOACs and conventional anticoagulation, respectively (OR 0.60, 95% CI 0.30 to 1.21; I-squared 0%). CRB occurred in 14.9 and 16.6% of patients receiving NOACs and conventional treatment, respectively (OR 0.88, 95% CI 0.57 to 1.35; I-squared 0%).



VTE recurrence with NOACs and cancer

Conclusions: NOACs seems as effective and safe as conventional anticoagulant treatment for prevention of VTE in cancer patients. Ad hoc clinical trials should be conducted to confirm these results.

4847 | BEDSIDE
Risk of myocardial infarction in patients treated with oral anticoagulation, a bayesian network meta-analysis

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Purpose: The relative safety of oral anticoagulants continues to be debated, and whether advances have been made in this regard with novel oral anticoagulants is unknown. The authors investigated the relative safety and efficacy of different oral anticoagulants (vitamin K antagonist warfarin, direct trombin inhibitor dabigatran and ximelagatran and activated X factor antagonist apixaban, rivaroxaban and edoxaban) in patients with indication for long term anticoagulation using a network meta-analysis.
Methods: Randomized controlled trials comparing novel anticoagulants to warfarin were searched using MEDLINE, EMBASE, and Cochrane databases. Information on study design, inclusion and exclusion criteria, sample characteristics, and clinical outcomes was extracted. The primary end-point of the analysis was the occurrence of myocardial infarction (MI). We performed a random-effects model within a Bayesian framework using Markov Chain Monte Carlo simulation to calculate pooled odds ratio (OR) and 95% credibility intervals (CI). We also ranked therapies by their likelihood of leading to the best results for the outcomes.
Results: Twelve trials including 100,524 randomized patients were analyzed. At the longest available follow-up the odds for MI was lower with warfarin when compared to dabigatran, ximelagatran and rivaroxaban and higher with apixaban and edoxaban (OR: 0.51 CI: 0.09-1.44, OR: 0.72 CI 0.12-1.98, OR: 0.79 CI: 0.12-2.29, OR: 1.17 CI 0.16-4.04, OR: 1.64 CI 0.12-7.16, respectively). In the Bayesian network analysis the posterior probability of being the first best choice of treatment was 33.3% for edoxaban, 26.3% for apixaban, 17.6% for warfarin, 11.7% for rivaroxaban, 2.71% for dabigatran and 8.3% for ximelagatran. Exclusion of the withdrawn ximelagatran and analysis with the corrected values of MI in the RELY trial did not substantially influenced the results.
Conclusion: There is a considerable heterogeneity regarding cardiac safety among oral anticoagulants. Differences in risk of myocardial infarction may influence the choice of treatment.

4848 | BEDSIDE
Are the guidelines recommendations followed in the clinical practice in patients with atrial fibrillation undergoing coronary stenting?

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Background: Patients with atrial fibrillation (AF) submitted to PCI and stenting (PCI-S) have an increased risk of bleeding due to the combination of dual antiplatelet therapy (DAPT: aspirin and clopidogrel) with anticoagulation (TT: triple therapy). The use of TT is a class IIb recommendation of the ACC/AHA/ESC guidelines. Other recommendations such as the use of drug eluting stent (DES), radial arterial access and closure device in femoral access are preferred.
Aim: To assess the adherence to guidelines recommendations.
Methods: A prospective multicenter study was conducted from 2007 to 2011 including patients with non-valvular AF who underwent PCI-S. Baseline characteristics, CHADS2, CHA2DS2VASc, HAS-BLED scores, PCI details, antithrombotic therapy at discharge and its duration were recorded. Follow-up was 1 year. All bleeding events, thromboembolisms (stroke or systemic embolism, acute myocardial infarction or target revascularization), total deaths, and cardiovascular deaths were analyzed post hoc.
Results: We identified 640 patients with AF and 320 (50%) of them were $\geq$75 years (79.8$\pm$5.6 years). The 74.2% had HTA, 48.3% were smokers, 37.0% diabetes mellitus, 55.2% dyslipidemia, 15.9% renal failure, 13.3% peripheral arteriopathy, and 32.0% previous ischemic heart disease. 419 patients (65.5%) had a CHADS2 score $\geq$2, 466 (73%) a CHA2DS2VASc $\geq$2 and 164 (25.6%) had a HASBLED $>$3. DES was implanted in 247 (38.6%) patients, in 328 (51.3%) radial access was chosen and only in 61 (9.5%) of patients submitted to femoral access a closure device was used. At discharge, 320 (50.2%) patients received TT, 266 (41.8%) DAPT and 50 (7.9%) warfarin plus clopidogrel. Total Bleedings occurred in 116 patients (18.1%), and 37 (5.8%) of them were major bleedings. Bleedings occurred mainly in patients treated with warfarin plus clopidogrel (20.9% TT vs 13.5% DAPT vs 26% warfarin plus clopidogrel, p=0.02). During follow-up, 64 patients (9.9%) died for any cause, and 47 (7.7%) because of a cardiovascular event. A multivariate analysis identified as predictors of cardiovascular mortality the age (OR: 1.05; 95% CI 1.00 to 1.11, p=0.043), renal failure (OR 6.24; 95% CI 2.77 to 14.06, p=0.0001), and the use of warfarin plus clopidogrel (OR 4.62; 95% CI 1.68 to 12.7, p=0.03). DES, the arterial access or the use of closure devices were not predictors.
Conclusions: In patients with AF submitted to PCI-S, guidelines recommendations are not always followed. The use of warfarin plus clopidogrel was associated to mortality while other recommendations such as DES, type of arterial access or closure devices had no effect.

WAYS TO IMPROVE CARDIAC SCREENING IN ATHLETES

4861 | SPOTLIGHT
Improving screening methods for detection of pediatric hypertrophic cardiomyopathy

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Introduction: Electrocardiogram screening in the pediatric population has been a very debated topic in recent times. The goal of this study was to demonstrate the utility of a vectorcardio-graphic parameter, the spatial peaks QRS-T angle, as compared to traditional 12-lead ECG criteria in the detection of pediatric hypertrophic cardiomyopathy (HCM). The spatial peaks QRS-T angle will outperform the Italian Pre-participation Screening Programme criteria for detecting pediatric hypertrophic cardiomyopathy.
Methods: 362 total patients were evaluated. 120 previously diagnosed, per echocardiographic criteria, pediatric HCM patients (median age 15 years) were assessed during routine cardiology follow-up appointments. Their results have been compared to those from 242 age/gender-matched control patients with normal echocardiograms (median age 13 years). The vectorcardio-graphic parameter, the spatial peaks QRS-T angle was derived from conventional 12-lead ECG recordings based on the method described by one of the co-authors et al. Intra-study sensitivity and specificity of traditional "pooled" 12-lead ECG criteria for HCM, using Italy's National Pre-participation Screening Programme criteria, were compared against results from the derived spatial peaks QRS-T angle. Paired T-tests were used to evaluate differences in the spatial peaks QRS-T angles between the HCM and age-matched control patients. Odds ratio and relative risk were also calculated.
Results: Mean values for spatial peaks QRS-T angles are 119.4$\pm$43.4 degrees for HCM, and 21.3$\pm$13.7 degrees for control patients. Significant differences existed between control versus HCM patients ($P<0.0001$). Utilization of the spatial peaks QRS-T angle (greater than 2 standard deviations above the mean angle for controls, 48.7 degrees) yields greater sensitivity and specificity for detecting HCM than the Italian Programme's pooled conventional ECG criteria. The Italian criteria yields a sensitivity and specificity of 66.7% (reported 70%) and 30.2%, respectively; the spatial peaks QRS-T angle at a cut off of $>$48.7 degrees has a sensitivity of 93.3% and a specificity of 97.9%. The Spatial QRS-T angle odds ratio was 550.7 (95% CI 186.6 to 1625.0) with a relative risk of 28.5 (95% CI 14.4 to 56.4). For the Italian criteria the odds ratio was 0.96 (95% CI 0.8 to 1.1) with relative risk of 0.96 (95% CI 0.8 to 1.1).
Conclusion: In our cohort, the spatial peaks QRS-T angle has better study sensitivity, specificity as well as relative risk stratification for detecting HCM than pooled conventional ECG criteria.

4862 | BEDSIDE
ECG abnormalities in athletes-prevalence and outcome of athletes with inverted T-waves

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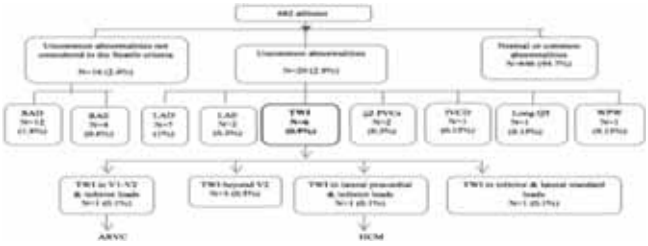
Purpose: Evaluate the prevalence of the abnormal ECG findings, according to the Seattle criteria (Sc), detected during the preparticipation screening program in a population of highly-trained athletes and identify those harbouring potential malignant cardiovascular diseases in a retrospective follow-up study.
Methods: We studied 682 Caucasian asymptomatic athletes (mean age 20.5±4.8 years, 459 males, 223 females). Mean follow-up was 12±3 years with a yearly screening program. Abnormal ECGs were identified and the presence of cardiomyopathies or primary electrical diseases was evaluated.
Results: In 20 (2.9%) athletes abnormal ECGs appeared. In 640 (93.8%) athletes, ECGs were normal or showed common abnormalities, while 22 (3.2%) athletes present uncommon ECG abnormalities, not certainly associated with inherited cardiovascular diseases, and thus not included in the Seattle criteria. Abnormal ECGs (Sc) included: negative T-waves in ≥2 adjacent leads in 6 (0.9%), intraventricular conduction delay ≥140 ms in 1 (0.1%), left QRS axis deviation in 7 (1%), left atrial enlargement in 2 (0.3%), ventricular pre-excitation pattern in 1 (0.1%), long QTc interval in 1 (0.1%), ≥2 premature ventricular contractions in 2 (0.3%). Two athletes (0.3%) with inverted T-waves were diagnosed with ARVC and HCM respectively during follow-up (Picture).



TWI may be a marker of cardiomyopathy.

Conclusions: Abnormal ECGs according to the Sc were present in 2.9% of our higly-trained athletes. Follow-up showed that 0.3% of athletes (2/682) presenting pathological inverted T-waves were diagnosed with cardiomyopathy and had affected first-degree relatives that were identified through clinical family screening, while athletes with normal ECG did not present any diagnostic criteria of cardiomyopathy.

4863 | BEDSIDE
High prevalence of malignant early repolarisation patterns in indigenous Australian and Pacific Islander/Maori athletes

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Electrocardiographic early repolarisation pattern (ERP) is a common finding in athletic populations. Certain patterns of ERP, namely inferior ERP with a horizontal ST-segment and/or marked J-wave amplitude have been termed "malignant" given their association with increased risk of sudden cardiac death. ERP is more common in black African than Caucasian (C) individuals. However, there is currently little data on the prevalence of ERP in athletes of other ethnic backgrounds, including Indigenous Australian/Torres Strait Islander and Pacific Islander/Maori (ATSPI) individuals. From June 2011 to December 2013, 843 C and 160 ATSPI elite male athletes underwent ECG screening. ECGs were analysed for the presence of ERP, defined as J-point elevation of at least 0.1mV in 2 or more inferior (II, III, aVF) or lateral (I,aVL, V4-V6) leads. J-waves were coded as notched, slurred or discrete, J-wave amplitude was measured and ST-morphology coded as horizontal or ascending. Heart rate, QRS duration and Sokolow-Lyon LVH scores were measured. Demographic differences between ATSPI and C are shown in Table 1. ERP was more common in ATSPI than C, as was inferior ERP, inferior ERP with a horizontal ST-segment and inferior ERP with a J-wave ≥2mm amplitude. Lateral ERP occurred with similar prevalence in both groups (Table 1). ERP, including ERP patterns associated with an increased risk of SCD are common in elite athletes, and significantly more prevalent in ATSPI than C athletes. The long-term clinical significance of ERP in this population is yet to be determined.

Table 1

	Caucasian males (n=843)	ATSPI males (n=160)	p value
Age (years)	20.4±4.2	20.2±3.7	0.574
Body surface area (m^2)	2.05±0.17	2.12±0.23	<0.0001
Heart rate (beats per minute)	58.4±10.4	62.9±11.3	<0.0001
QRS duration (ms)	97.7±9.6	95.4±9.9	0.0058
Sokolow Lyon score (SV1+RV5, mV)	3.1±0.9	2.8±0.8	<0.0001
Inferolateral ERP	149 (17.7%)	46 (28.8%)	0.0017
Inferior ERP only	75 (8.9%)	31 (19.4%)	<0.0001
Lateral ERP only	104 (12.3%)	12 (7.5%)	0.1054
Inferior ERP with horizontal ST-segment	143 (17%)	61 (38.1%)	<0.0001
Inferior ERP with J-wave amplitude ≥ 2mm	73 (8.7%)	28 (17.5%)	0.0011

ERP, early repolarisation.

4864 | SPOTLIGHT
Coronary artery disease in asymptomatic male athletes aged 45 years or older with a low ESC SCORE risk: the emerging role of coronary CT angiography

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Purpose: Over 90% of exercise related cardiac arrests occur in men aged 45 years or older, in whom coronary artery disease (CAD) is the main cause. The current cardiovascular evaluation of middle-aged recreational athletes essentially consists of a medical history, physical examination, resting and exercise electrocardiography. Coronary computed tomography angiography (CCTA) provides a minimally invasive, low radiation dose opportunity to image the coronary arteries. We aim to assess the feasibility and added value of CCTA in asymptomatic male recreational athletes aged ≥45 years who underwent a sports medical evaluation.
Methods: 320 participants underwent prospective ECG-triggered CCTA using a 256-slice CT scanner. After exclusion of 44 participants with diabetes, hypertension, or an ESC risk score >4% a group of 276 men with a low SCORE risk (0-4%) remained in whom the presence of CAD was defined as a Coronary Artery Calcium Score (CACS) ≥100 Agatston Units or ≥50% luminal stenosis.
Results: In 41 (15%, 95% CI 10.8 – 19.1) of 276 participants with a low ESC SCORE risk and good exercise tolerance (see table), relevant CAD (CACS ≥100 or luminal stenosis ≥50%) was found. The number needed to screen was 6.7.

N = 276	Mean	Range
Age (years)	54,2±6,3	45–72
Systolic BP (mmHg)	127,6±12,6	100–168
Diastolic BP (mmHg)	79,2±8,5	40–100
BMI (kg/m^2)	24,8±2,7	18,8–37
Total cholesterol (mmol/l)	5,4±0,9	2,92–7,7
SCORE (%)	1,57±0,9	0–4
Total workload (W)	318,7±45	210–450
Workload (W/kg)	3,8±0,8	2,3–5,3
Radiation dose (mSv)	3,84±0,9	2,4–5,6
CACS (AU)	62,3±193,8	0–1728
Coronary artery disease, n (%)	41 (15)	

Conclusion: Minimally invasive CCTA is feasible and detects relevant coronary artery disease in 15% of asymptomatic male athletes ≥45 years with a low ESC SCORE risk and normal exercise testing.

4865 | BEDSIDE
Cardiovascular screening in middle-aged individuals engaged in high intensity sport activities: implications, yield and cost-analysis

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Purpose: The European Association of Cardiovascular Prevention and Rehabilitation (EACPR) has recently edited the recommendations for cardiovascular screening in middle-aged individuals engaged in sport activities. However, very few data exist concerning the impact of such position stand. Our study aimed to assess implications, yield and costs of this preventive evaluation.
Methods: We conducted a prospective observational multicenter study including individuals aged 35 to 65 years engaged in high intensity sport activities and free from cardiac diseases. Athletes were examined following the EACPR protocol including history, physical examination, 12-lead resting electrocardiogram (ECG) and risk stratification according to the Systematic Coronary Risk Evaluation (SCORE). Athletes with abnormal findings at screening or at high cardiovascular risk underwent additional examinations. The costs of the overall screening program until diagnosis were calculated according to Swiss medical rates.
Results: From January to December 2013 we enrolled 761 athletes (73% males, 46.8±7.3 years). Running (33%) and cycling (23%) represented the most popular sports. The mean training volume during the last year was 5.7±4.1 hours/week. A total of 110 athletes (14.4%) required additional examinations: 13 (1.7%) due to history, 34 (4.5%) due to physical examination, 40 (5.3%) because of abnormal ECG and 32 (4.2%) due to high cardiovascular risk (SCORE system). A previously unknown cardiovascular abnormality was established in 20 (2.6%) athletes, severe hypercholesterolemia (>8 mmol/l) in 8 (1.0%) athletes while type 2 dia-

betes was discovered in 1 (0.1%) athlete. Three (0.4%) athletes were considered not eligible for high intensity physical exercise (due to hypertrophic cardiomyopathy, old myocardial infarction with ventricular arrhythmia and 50 mm aneurysm of ascending aorta). The cost was 111'775 Euros (€) for the overall program, 147 € per athlete and 3'854 € per finding.
Conclusions: Cardiovascular screening in middle-aged athletes allows the detection of a significant number of new cardiovascular abnormalities and major cardiovascular risk factors, precluding in selected cases high intensity physical exercise. The overall screening program seems to be feasible at reasonable costs.

4866 | BEDSIDE
Sudden cardiac death in young athletes - data from the Swiss registry

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Purpose: Sudden cardiac death (SCD) in young athletes is of great public interest. In Switzerland systematic pre-participation screening (PPS) including an ECG exist only for professional athletes in high risk sports like ice hockey or football. The purpose of this study was to analyze the incidence and causes of SCD in this population.
Methods: In a retrospective cohort study we reviewed all forensic reports between 1999 and 2010 of German-speaking parts of Switzerland (with an overall population of 5'617'963) for SCD in young individuals (10-39 years). Data were collected in the Swiss REGistry of Athletic Related Death, swissregard.ch. SCD was divided into the following categories: not-related to sports (NON), during recreational sports (REC), and in competitive sports (COMP). Further subdivision of COMP was made into professional and non-professional athletes. The denominators for the calculation of incidences were derived from the Federal Offices of Statistics and Sports.
Results: In the 11-year period under investigation, a total of 267 (76.5%) males and 82 (23.5%) females succumbed to SCD. Of these, 52 (14.8%) were sports-associated SCDs with male predominance (92.3% male versus 7.7% females). 31 (59.6%) athletes died during REC and 21 (40.4%) during COMP. Of those, 3 (14.3%) were professional athletes. Median age [interquartile range] in NON, REC, and COMP was 32 [10], 32 [15], and 30 [14] respectively. Incidence for NON SCD, REC SCD, and COMP SCD were 1.17/100'000, 0.21/100'000, and 0.57/100'000 respectively. Incidences of NON versus COMP, NON versus REC and REC versus COMP were significantly different (all $p<0.001$). SCD in COMP mostly occurred during ball games (55%), in REC mostly during endurance sports (68%). Underlying causes of SCD in COMP were coronary artery disease without acute myocardial infarction in 5 (23.8%) athletes, acute myocardial infarction in 3 (14.3%), dilated cardiomyopathy in 2 (9.5%), aortic valve stenosis in 2 (9.5%), and in one each (4.8%) due to hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and Wolff -Parkinson-White syndrome. SCD in the 3 professional athletes (aged 26, 28 and 30 years) were all due to acute myocardial infarction.
Conclusion: In this cohort, the incidence of sport-associated SCD was low, especially in professional athletes. Interestingly all SCD in this group were caused by acute myocardial infarction. It appears, that PPS with ECG in professional athletes in high risk sports may prevent SCD caused by inherited diseases, but does not to prevent SCD due to acute myocardial infarction.

ATRIAL FIBRILLATION: HOW TO IMPROVE PROGNOSIS?

4871 | BEDSIDE
Higher risk of death and stroke in patients with persistent versus paroxysmal atrial fibrillation: results from the ROCKET AF trial

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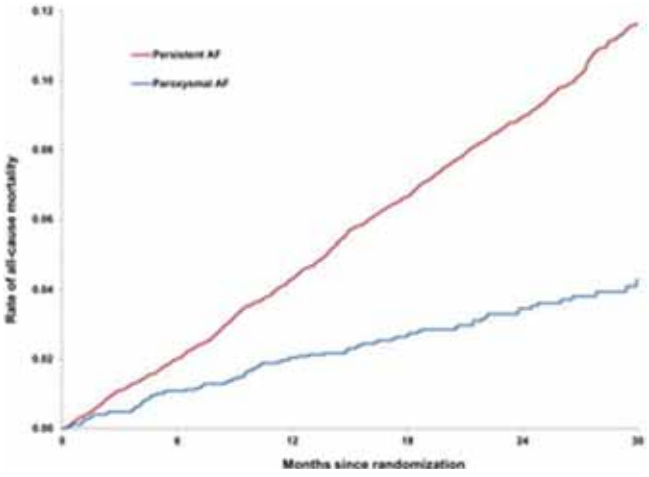
Purpose: Anticoagulation prophylaxis for stroke or systemic embolism is recommended for at-risk patients with atrial fibrillation (AF), regardless of whether it is paroxysmal or persistent. However, outcomes in anticoagulated patients with paroxysmal versus persistent AF are uncertain. We assessed the risk of stroke and death in patients with paroxysmal versus persistent AF receiving oral anticoagulation for stroke prophylaxis.
Methods: Patients randomized in the ROCKET AF trial (n=14,264) were grouped by baseline AF category: paroxysmal or persistent. Multivariable adjustment was performed to compare thromboembolic events, bleeding, and death between groups, in high-risk subgroups, and across treatment assignment (rivaroxaban or warfarin).
Results: Of 14,062 patients, 11,548 (82%) had persistent AF at baseline, and 2514 (18%) had paroxysmal AF. Patients with persistent AF were marginally older (73 vs. 72; p=0.03), less likely female (39% vs. 45%; $p<0.0001$), and more likely to have previously used vitamin K antagonists (65% vs. 56%; $p<0.0001$) compared with patients with paroxysmal AF. In patients randomized to warfarin, time in therapeutic range was similar (58% vs. 57%; p=0.94). Patients with persistent AF had higher adjusted rates of stroke or systemic embolism (2.18 vs. 1.73 events/100-pt-yrs; p=0.048) and all-cause mortality (4.78 vs. 3.52; p=0.006) (Figure). Rates of major bleeding were similar (3.55 vs. 3.31; p=0.77). Rates of stroke or systemic embolism in both AF types did not differ by treatment assignment (rivaroxaban vs. dose-adjusted warfarin; p interaction=0.6).



Conclusions: In patients with AF at moderate to high risk of stroke receiving anticoagulation, those with persistent AF have a higher risk of thromboembolic events and worse survival compared with paroxysmal AF.

4872 | BEDSIDE
The efficacy of apixaban compared to warfarin in patients with atrial fibrillation with high coagulation activity despite anticoagulant treatment

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Purpose: The aim was to compare the effect of apixaban to warfarin in relation to coagulation activity during treatment.

Abstract 4872 – Table 1

		Stroke/SEE (n=96)				Major/CS non major bleeds (n=379)			
		Apixaban, %/year Events/Patients	Warfarin, %/year Events/Patients	Apixaban vs Warfarin HR (95%CI)	*p	Apixaban, %/year Events/patients	Warfarin, %/year Events/patients	Apixaban vs Warfarin HR (95%CI)	*p
F1+2 (pmol/L)	≤75.9	0.62	1.03	0.60	0.8969	4.83	5.34	0.91	0.3025
		7/613	34/1818	(0.27–1.36)		51/612	162/1814	(0.61–1.24)	
	>75.9	1.07	1.89	0.56		3.78	5.34	0.71	
		36/1816	19/558	(0.32–0.98)		118/1851	48/556	(0.51–1.00)	
D-dimer (≤μg/L)	≤401	0.85	0.93	0.92	0.3652	3.00	4.58	0.66	0.4722
		17/1077	23/1355	(0.49–1.73)		57/1074	106/1353	(0.48–0.91)	
	>401	1.05	1.65	0.63		4.92	6.43	0.77	
		26/1396	30/1022	(0.37–1.07)		112/1389	104/1018	(0.59–1.00)	

*P-value for interaction between treatment and biomarker level.

Methods: In the ARISTOTLE trial 18201 patients with atrial fibrillation (AF) were randomized to apixaban 5 mg twice daily or warfarin. Of these patients 4850 were included in a biomarker study with blood sampling after 2 months of study treatment. Stroke/systemic embolism (SEE) and major/clinical significant (CS) non major bleed were evaluated after 2 months. The median follow-up time was 1.8 years. Cox models including treatment, biomarker level at month 2 and the interaction as covariates were analyzed.
Results: The median prothrombin fragment 1+2 (F1+2) and D-dimer levels at 2 months were 75.9 pmol/L and 401 μg/L, respectively.
Conclusion: High D-dimer and F1+2 levels despite oral anticoagulant treatment identify AF patients at high risk of stroke, and high D-dimer is also associated with risk of bleeding. The beneficial effects of apixaban compared to warfarin were consistent regardless of the coagulation activity evaluated during treatment.

4873 | BEDSIDE
Digoxin use in patients with atrial fibrillation is associated with adverse cardiac outcomes: results from the ROCKET AF trial

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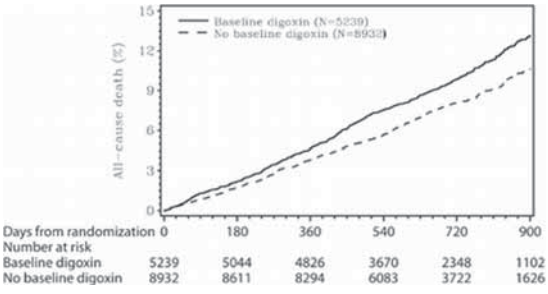
Purpose: Although no large clinical trial has randomly assigned and evaluated digoxin in patients with atrial fibrillation (AF), digoxin remains a guideline-recommended therapy in this population. We studied the use and outcomes of digoxin in patients with AF with and without heart failure (HF) in the context of a clinical trial aimed at stroke prevention.
Methods: Patients enrolled in ROCKET AF (rivaroxaban vs. dose-adjusted warfarin for stroke prevention) were included and categorized based on digoxin use at baseline and during the study. Cox proportional hazards regression models adjusted for baseline characteristics and medications were used to test the time-dependent effect of digoxin on all-cause, vascular, and sudden death. Cardiovascular outcomes were adjudicated as part of the trial.
Results: Of randomized patients (n=14,171), baseline digoxin use was reported in 5239 (37.0%). Patients treated with digoxin were more likely to be female (42.4% vs. 37.9%), have a history of HF (73.3% vs. 56.1%), have diabetes (43.0% vs. 38.0%), and have persistent AF (88.0% vs. 77.0%) ($p<0.001$ for each comparison). Kaplan-Meier curves for all-cause death are shown for patients with and without baseline digoxin. After adjustment, digoxin was associated with increased all-cause (HR 1.22; 95%CI 1.08-1.37), vascular (HR 1.22; 95% CI 1.05-1.42), and sudden death (HR 1.29; 95% CI 1.03-1.61). There was no significant digoxin-HF interaction for all-cause (p=0.79), vascular (p=0.78), or sudden death (p=0.56).



Conclusions: In ROCKET AF, digoxin therapy was associated with a significant increase in all-cause, vascular, and sudden death in patients with AF. These data do not support the routine use of digoxin in patients with AF with or without HF and suggest the need for re-evaluation of current recommendations.

4874 | BEDSIDE
Reduction in bleeding with edoxaban vs warfarin linked to lower all-cause mortality in 21,105 pateints randomized in the ENGAGE AF-TIMI 48 trial

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Background: Edoxaban was associated with significantly less bleeding and lower mortality as compared to warfarin in the ENGAGE AF-TIMI 48 trial of 21,105 patients with atrial fibrillation. The causes of death and relationship between bleeding and death have not been previously described.
Methods: ENGAGE AF-TIMI 48 was a double-blind trial comparing warfarin (TTR 68.4%), with 2 regimens of once-daily edoxaban (high-dose[HD], low-dose[LD]) over a median follow-up of 2.8y. We analyzed the data on the cause of death and relationship to bleeding as adjudicated by the independent, blinded, clinical endpoint committee (CEC). The CEC determined whether deaths were directly due to a bleed (i.e, fatal bleed), bleeding contributed to death, or death was not directly related to bleeding. Major bleeding was defined per ISTH criteria.
Results: There were 839 deaths (4.35%/yr) in the warfarin arm, compared with 773 deaths (3.99%/yr, p=0.08) with HD edoxaban, and 737 deaths (3.80%/yr, p=0.006) with LD edoxaban. Reductions in fatal bleeding represented 45% and 40% of the excess in deaths with warfarin compared to HD and LD edoxaban, respectively (Table). The total of fatal bleeding, deaths in which bleeding was a contributing factor, and deaths in patients who had a non-fatal major bleed represented 89% and 86% of the excess in deaths observed in the warfarin arm, as compared to HD and LD edoxaban regimens, respectively.
Conclusions: The majority of the reduction in all-cause mortality observed with edoxaban in the ENGAGE AF-TIMI 48 trial was either directly or indirectly associated with lower rates of fatal or non-fatal major bleeding with edoxaban as compared to warfarin.

4875 | BEDSIDE
Time-dependent rate of events after coronary stent implantation in patients with atrial fibrillation

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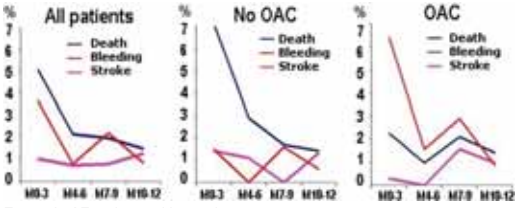
The optimal regimen of the antithrombotic therapies in patients with atrial fibrillation (AF) who have had a coronary stent is unclear. The incidence of the several cardiovascular events may vary over the first year in these patients, some of whom being greatest in the first months after stent implantation. We tried to evaluate this time dependency and how oral anticoagulation (OAC) may affect the rate of these different events.
Methods: All patients with AF and stent implantation seen between 2000 and 2010 in 3 academic hospitals were identified and followed up for events in each period of 3 months for 12 months.
Results: In 978 AF patients with coronary stent placement (mean age 72, 72% male, CHADS2 score 2.0), OAC was prescribed on an individual basis for 417 patients (43%) and no OAC in the remaining 561 patients (57%). During a 1-year follow-up, we found that the rate of stroke in % was relatively stable during the follow-up, whilst death was the predominant event in 1st trimester. Rate of bleeding events was highest in first 3 months after stent implantation. Therapy with OAC was associated with a lower all-cause mortality in the periods 0-3 months



Events in AF patients with stenting.

Abstract 4874 – Table 1. Relationship between deaths and bleeding

	Warfarin (N=7046)	HD Edox (N=7035)	Diff, HD vs warfarin, n (%)	P, HD Edox vs warfin (N=7034)	LD Edox n (%)	Diff, LD vs warfin,	P, LD Edox vs warfin
Total deaths	839	773	–66 (100%)	0.082	737	–102 (100%)	0.006
Fatal bleeds	65	35	–30 (45%)	0.003	24	–41 (40%)	<0.001
Bleed contrubted to death	36	24	–12 (18%)	0.12	30	–6 (6%)	0.44
Death not directly due to bleed	738	714	–24 (36%)	0.47	683	–55 (54%)	0.10
Non-fatal major bleed prior to death	99	82	–17 (26%)	0.20	58	–41 (40%)	0.001
No major bleed prior to death	639	632	–7 (11%)	0.77	625	–14 (14%)	0.57

HD: high-dose edoxaban regimen (60 mg QD; 30 mg QD if creatinine clearance <50 mL/min, weight <60 kg, or on a potent P-gp inhibitor. LD: low-dose edoxaban regimen (30 mg QD; 15 mg QD of any of the above 3 criteria).

(p=0.0003) and 3-6 months (p=0.04) but with a higher risk of bleeding over the same periods (p=0.0001 and p=0.003 respectively) and a stable and similar rate of stroke (2.9% vs 3.8% after 1-year FU in patients with OAC and no OAC respectively, p=0.48) (figure). This resulted in a lower mortality at 1 year in patients treated with OAC (6.6% vs 12.6%, p=0.002)

Conclusions: In one of the largest series of AF patients with coronary stent implantation, prescription of OAC was associated with a significantly lower mortality in first months but a higher risk of bleeding. The initial benefit on survival was still significant after 1-year follow-up.

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The french screening campaign of atrial fibrillation in general practice: assessment of predictive criteria for atrial fibrillation

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Purpose: Atrial fibrillation (AF) affects nearly 750 000 patients in our country and this number is expected to double by 2050. AF is a severe disease with important consequences in terms of morbidity and mortality but still under-diagnosed. Boehringer ingelheim deployed in 2013 an AF screening campaign (profil FA) among family physicians in 16 national sites with a simple questionnaire based on heartbeat measurement, AF linked symptoms and thromboembolic patient risk.
The main objective of this evaluation was to identify the most predictive factors of the disease to provide a simple tool to improve screening and diagnosis of AF in patients over 65.
Methods: Main predictive factors of AF were identified, from questionnaire results, using a logistic regression model. A prognostic score was estimated and its predictive performance investigated using the ROC curve.
Results: 4592 patients were screened, 585 were oriented to a cardiology specialist and 129 were diagnosed with AF. The statistical analysis was performed on the sample of oriented patients The logistic regression model identified 3 predictive factors of AF: irregular heartbeat (OR=12.0, p<0.0001), history of stroke, transient ischemic attack or peripheral embolism (OR=2.0, p=0.07) and presence of at least two of the following symptoms: faintness, palpitations, chest pain and shortness of breath (OR=2.3, p=0.0008). An AF prediction based only on irregular heartbeat (1st criteria) showed a sensibility of 74.2% and a specificity of 81.9%, its positive predictive value was 55,6%. It represents the main predictive criteria of AF.
Improving the tool by adding screening based on the presence of at least two symptoms in patients having a thromboembolic history improves sensibility (80.0%) while maintaining good specificity (79.4%).
Screening campaign showed that applying strictly those latest criteria to patients of the screened cohort could have potentially led to diagnosis of 75 additional AF. However 24 patients (all with regular heartbeats) with FA would have been missed
Conclusion: The measure of heartbeat is the main predictive criteria in patients over 65, as pointed in ESC 2012 guidelines, but patients with a regular heartbeat should also be considered. They should systematically be referred to a cardiologist in case they present at least two symptoms and a thromboembolism history of unknown origin. The campaign underlined the difficulty to diagnose AF in patients having a regular heartbeat which should encourage systematic heartbeat measures and identification of at risk patients feeling palpitations.

MANAGEMENT OF IMPLANTABLE CARDIOVERTER DEFIBRILLATOR ON SPECIFIC POPULATIONS

P4877 | BEDSIDE

Management of implantable defibrillators (ICD) in end of life situations: is deactivation considered? and who makes the decision?

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Management of ICD therapies in terminal patients or patients with a bad quality of life is a complex issue. About 33% of the patients implanted with an ICD can receive painful and stressing shocks in the last day of life if those therapies are not deactivated. Recent expert consensus statements have been published by the American and European Societies of Cardiology recommending deactivation options to be discuss beforehand.
Purpose: To know physician attitudes and real life management of terminally ill patients with an ICD: is deactivation considered, is the patient informed about this possibility and when is it discussed.
Methods: A survey was undertaken among all the implanting centers in a European country. Questions asked were related to the awareness of recent recommendations, number of ICD deactivated in the last year, at what point in the medical history was the possibility of device deactivation discussed and who made the decision. Ideal moment for the talk about deactivation options was also requested. Centers were classified as high implant when implanting 100 or more devices a year, medium 50-99 and low implant rate <50.
Results: 100% (8) of the high, 84% (21) of the medium and 10% (13) of the low volume centers answered the survey. Only 44% of the professionals were aware of the recommendations made by the scientific societies, independently of the volume of implants in the center. The total number of ICDs deactivated per center was low (no center deactivated more than 5 devices in 2012). 3 Centers discuss deactivation early (before implant or during clinical visits), 17 in terminally ill patients, 7 in terminally ill with frequent shocks and 16 centers never discuss it. The patients take part in the decision in only 52% of the centers. When asked about the ideal moment to discuss deactivation possibilities 17 centers answered that it should be done early, 13 only in terminally ill patients, 9 in terminally ill patients with frequent shocks and 3 centers answered that deactivation should never be discussed.
Conclusion: Physician attitudes and real life management of terminally ill patients with an ICD differ substantially from the recommendations made by scientific societies. Implanting physicians recognize that deactivation options should be discussed earlier in the clinical history of their patients than it is nowadays done. In only 52% of the cases was the patient part of the discussion and the decision to deactivate.

P4878 | BEDSIDE

Influence of young age on adverse outcomes of the subcutaneous implantable cardioverter defibrillator

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Purpose: The new subcutaneous implantable cardioverter-defibrillator (S-ICD) eliminates the need for transvenous leads, and therefore has the potential to reduce long-term complications by elongating lead-longevity, which is particularly interesting for younger ICD patients who are at increased risk of ICD-related complications. It is however unknown whether young S-ICD patients are more at risk for short-term complications.
Methods: From the largest S-ICD implanting center worldwide, we compared ICD harm (i.e. inappropriate shocks and/or complications) in patients < and >50 years (yrs) in our S-ICD registry, which collects consecutive S-ICD implantation information plus follow-up data.
Results: A total of 82 S-ICD patients were included, of whom 62 were <50 yrs (53% male, age 34±10 yrs) and 20 >50 yrs (50% male, age 58±7 years). During a follow-up of 23±14 months 7 (11%) patients <50 yrs and 2 (10%) patients >50 yrs had inappropriate shocks (p=1.00), of which 5 and 1 were due to T-wave oversensing respectively. Complications occurred in 6 (10%) patients <50 yrs and 2 (10%) patients >50 yrs (p=1.00). The composite endpoint of ICD harm occurred in 12 (19%) patients <50yrs and 3 (15%) patients >50 yrs (p=1.00). The probability of S-ICD harm at 2 years was 22% in patients <50 years and 18% in patients >50 years (figure, log-rank p=0.69).

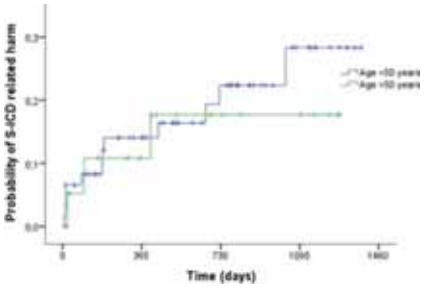

Figure 1

Conclusion: In contrast to transvenous ICDs, there is no difference in the probability of short-term ICD-related harm after 2 years in S-ICD patients <50 yrs vs. >50 yrs. Therefore, the potential benefit of the S-ICD to reduce long-term complications for young patients is not overshadowed by a higher rate of short-term complications.

P4879 | BEDSIDE

Inappropriate shocks are more common in asymptomatic vs symptomatic Brugada syndrome patients implanted a cardioverter-defibrillator

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Background: Brugada syndrome (BrS) is an inherited arrhythmogenic disease causes sudden cardiac death (SCD) particularly in young people. Implantable cardioverter-defibrillator (ICD) remains the recommended treatment for secondary prevention. Despite confident data against this approach, some asymptomatic, the so-called "high risk", patients are still being implanted an ICD, regardless of the high rate of device complications. We compared the occurrence of major complications in consecutive BrS patients implanted an ICD.
Method and results: Consecutive Patients implanted an ICD for primary or secondary prevention of BrS were studied. The diagnosis of BrS was based on

symptoms (syncope or cardiac arrest) in conjunction with the ECG type 1 pattern, either spontaneous or unmasked by drug challenge. Per- and post-implantation complications, and ICD programming controls were recorded. All patients underwent ICD control every 6 months or less depending of device-related event. Patients or relatives were also contacted by telephone to check last news (alive or died). We studied 46 patients (mean age of 46.7±10.5 years, 10% of female). Spontaneous type 1 ECG pattern was found in 37 (80.4%) of patients and atrial fibrillation in 5 (10.9%). Prior to ICD implantation, No symptom, Syncope, and aborted cardiac arrest were found in 15 (32.6%), 23 (50%), and 8 (17.4%) patients respectively. During a median follow-up period of 76±41.7 months (at 1 to 192), appropriate ICD shocks occurred in 10 (21.7%) patients of whom 90% had spontaneous coved type ECG, 40% had previous syncope and 60% already have experienced aborted SCD. Five (10.9%) patients had had inappropriate shocks (IS), of whom 3 (60%) in asymptomatic and 40% in syncope groups. Other Complications were reported in 10 (21.7%) patients. Lead fracture, Lead dislodgement, pneumothorax, pocket infection, myocardial perforation, and re-operation for any reason occurred in 4 (8.7%), 2 (4.3%), 1 (2.2%), 1 (2.2%), 1 (2.2%), and 9 (19.6%) respectively. The incidence of IS is higher in asymptomatic vs symptomatic patients if we consider the confidence interval of 90% (p=0.09) in this rare disease, whereas other complications had similar rate occurrence.

Conclusion: ICD was shown to be an effective therapy in symptomatic patients, particularly in those with previous cardiac arrest. However, the high rate of device complications, mainly inappropriate therapies recommends to accurately assess the risk-benefit of cardioverter-defibrillator and avoid this treatment in asymptomatic patients.

P4880 | BEDSIDE
Complications 1 year after generator only and combined generator and lead replacement operations

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Purpose: CIED implantations continue to rise. With an aging population, at least 1 generator replacement ± lead can be expected during their lifetime. Although considered a greater risk for revision than index implants, evidence is scant. We present complication rates for generator only (Bx) and generator+lead operations (Bx+lead).

Methods: Consecutive Bx and Bx+lead operations between April 2008 - March 2011, were followed for complications within 1-year. Complications recorded were; 1) any device-related return to theatre within 1 year, with 2) pneumothorax and 3) pericardial effusion additional for Bx+lead procedures. Deaths within 1 year were recorded.

Results: 805 Bx procedures were performed (12 AAI, 156 VVI, 484 DDD, 28 VR, 64 DR, 16 CRTP, 45 CRTD) and 111 Bx+lead (37 Bx+atrial, Bx+A; 34 Bx+ventricular, Bx+V; 5 Bx+A+V; 27 Bx+defibrillator, Bx+ICD, 1 Bx+A+ICD; 6 Bx+coronary sinus, Bx+CS and 1 Bx+CS+ICD). Male patients constituted 55.3% Bx and 59.5% Bx+lead procedures. Bx median age was 76 yrs and Bx+lead 69 yrs. 4.2% Bx and 9.9% Bx+lead procedures were performed acutely. Table 1 demonstrates complications according to Bx and Bx+lead.

Table 1. Bx and Bx+lead 1 year complications

	Bx (n=805)	Bx+lead (n=111)
Pneumothorax	–	5
Pericardial effusion	–	2
Haematoma surgical evacuation	0	1
Reburial	21	7
Lead intervention	8	5
Extraction	20	5
Re-implant	17	4
Upgrade	5	2
Total	71 (8.8%)	31 (27.9%)

All Bx+lead extractions were for infection, with Bx only extractions for infection (18), a dysfunctional unit (1) and radiotherapy treatment (1). Bx+lead complications by lead intervened upon; Bx+A 48.6% (n=37), Bx+V 26.5% (n=34), Bx+ A+V 20.0% (n=5), Bx+ICD 3.7% (n=27), Bx+CS 33.3% (n=6)and 0% Bx+A+ICD (n=1) and Bx+CS+ICD (n=1).

Conclusion: Complication rates for Bx and Bx+lead procedures are 8.8% and 27.9%. Atrial, ventricular or atrial plus ventricular lead procedures should be considered greater risk.

P4881 | BEDSIDE
Chronic kidney disease is an important predictor of complications after cardiac device implantation

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Purpose: In accordance with the increasingly broader criteria for device implantation, the number of cardiac devices implanted and its associated complications have become an important matter even in small centers (<100 procedures/year). The aim of this study was to assess potential predictors of complications in cardiac devices related procedures.

Methods: Retrospective, cohort study including all patients submitted to cardiac device related procedures between 2012-2013. Information regarding past medical history, chronic medication, motive for cardiac implantation device, type of procedure and cardiac device implanted were retrospectively collected. All patients were prospectively followed-up. Mortality and infectious and non-infectious complications were assessed. The primary endpoint was a combined endpoint including infectious and non infectious complications as well as mortality.

Results: Between January 2012 and December 2013, 230 patients were submitted to an invasive cardiac device related procedure. 155 (67,1%) procedures consisted of first device implantations, 34 (14,8%) were generator change procedures, 36 (15,7%) procedures related to upgrade simple pacemaker to resynchronization devices and only 5 (2,2%) procedures related to wire removal. Mean follow up time was 267 days. The primary endpoint was achieved in 38 (16,5%) patients. The prevalence of most cardiovascular risk factors was not statistically different between the group of patients with complications and without complications: hypertension (63,2% vs. 71,4%, p=0,336); Type 2 Diabetes Mellitus (34,2% vs. 33,9%, p=1,00); Dyslipidemia (42,1% vs. 51,6%, p=0,375). The presence of chronic kidney disease (CKD) was significantly higher in the group of patients who had complications (18,4% vs.4,2%; unadjusted OR 2,79 (95% CI: 1,22–6,40), p=0,015). When we considered the presence of CKD and antiplatelet drug use together, they significantly predicted endpoint achievement at follow up (χ^2=7,292, df=2, n=230, p=0,026). Only the presence of CKD significantly contributed to the prediction model (presence of chronic kidney disease adjusted HR 2,385 (95% CI: 1,022–5,567, p=0,044) antiplatelet drug use adjusted HR=1,736 (95% CI: 0,870–3,464, p=0,117).

Conclusion: CKD is a significant predictor of a combined endpoint including mortality, non infections and infectious complications after cardiac device related invasive procedures.

P4882 | BEDSIDE
ICD benefit is greater in patients with a higher predicted proportion of sudden death: application of the Seattle Proportional Risk Model in a real world population

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Introduction: ICDs reduce sudden death (SD) by ~60% in clinical trials. The Seattle Proportional Risk Model (SPRM) is designed to predict the proportion of SD vs. non-SD using simple variables; age, gender, EF, NYHA, SBP, Na, Cr, DM, BMI, and digoxin use. It has been prospectively validated in SCD-HeFT and HF-ACTION.

Methods: All primary prevention ICD recipients of an university medical center since 1996 were included. The Seattle Heart Failure Score (SHFS) was used to adjust for heart failure severity. An interaction term was employed to ascertain if ICD benefit varied with SPRM adjusted for CRTD vs. ICD and QRS width. The SHFM estimated 5 year survival with medical therapy and the Kaplan Meier observed 5 year survival was used to estimate ICD/CRTD benefit.

Results: A total of 1969 patients were included (63±11yrs; 79% male; 58% CRT-D). The proportion of patients with a CRTD decreased as the SPRM increased (74%, 60%, 54%, 46%). In a Cox Model, ICD/CRTD benefit varied with SPRM (HR 0.80; p=0.05). Figure 1 illustrates HR estimates for SPRM quartiles. Device benefit was greatest in those with a higher predicted proportion of SD. Estimated HR for SPRM >median (50% predicted proportion of SD) was 0.74 (p=0.045) vs. those with SPRM <50%. The estimated HR using the SHFM as a virtual control group for SPRM<50% (50%), the estimated HR was 0.54 for ICD and 0.56 for CRTD.

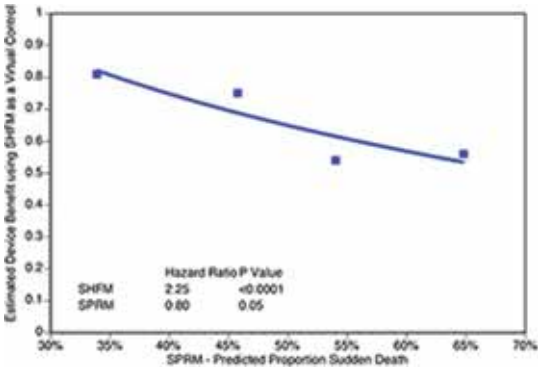

Figure 1

Conclusion: The benefit of ICD & CRTD varies with the SPRM predicted proportion of SD with greater benefit in those where the predominant mode of death is SD (>50%). This observational dataset validates the concept that SPRM may be useful in selecting patients for ICDs.

P4883 | BEDSIDE

Implantable defibrillator early after primary percutaneous intervention for ST-elevation myocardial infarction: the Defibrillator After Primary Angioplasty (DAPA) trial

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Purpose: It is not known which patients after primary Percutaneous Coronary Intervention (PCI) for ST elevation myocardial infarction (STEMI) have survival benefit of prophylactic implantable cardioverter defibrillator (ICD). The aim of the DAPA trial is to evaluate the efficacy and safety of ICD in high risk patients after primary PCI for STEMI.
Methods: A prospective randomized, multicenter controlled study to compare ICD plus conventional medical therapy vs. conventional medical therapy alone in patients with primary PCI for STEMI. Inclusion criteria were TIMI flow less than 3 after primary PCI or left ventricular ejection fraction lower than 30%. ICD was implanted between 30 and 60 days after the index STEMI. Primary endpoint was all-cause mortality after at least 3 years follow-up.
Results: After inclusion of 266 patients, enrollment was stopped after advice of the data safety board. Mean age was 60.8±11.3 years, 78.2% was male. Baseline characteristics were comparable between the two treatment groups. Cross-over was 15.6% in the non-ICD group and 2.3% in the ICD group. During a median follow-up of 5.5 years (IQR 3.0-7.4 years) 40 patients achieved the primary endpoint which was significantly lower in the ICD-group vs. the conventional group (11.2% vs. 21.1% p=0.036). Documented sudden cardiac death was 1.6% in the ICD group versus 4.9% in the non-ICD group (p=0.172).
Conclusion: In patients with a high risk of death after primary PCI for STEMI, ICD lowers long-term mortality. However the results of this trial should be interpreted cautiously, since the study was stopped prematurely.

IMPORTANT INFLUENCES OF HEART FAILURE MANAGEMENT

P4884 | BEDSIDE

Prognostic role of atrial fibrillation in patients affected by chronic heart failure: a matching group analysis

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Purpose: Atrial fibrillation (AF) is common in heart failure (HF), but it remains unclear whether the adverse role of AF is due to the arrhythmia itself or to its association with more severe HF status. Aim of the study was to investigate the prognostic role of AF in a population of chronic HF patients, comparing outcomes of patients with and without AF in the overall study population, and in two study cohorts of AF and sinus rhythm (SR) patients matched for established HF prognostic indicators.
Methods: We enrolled patients with a history of HF and reduced ejection fraction (EF), followed in 17 Italian HF centers. Patients were followed for 1307±945 days. The study endpoints were the composite of cardiovascular (CV) death and urgent heart transplant and all-cause death. Data analysis was performed considering 1) the entire population, divided according to the presence (n=565) or not (n=2882) of AF; 2) 1:1 statistical matching between SR and AF patients. Groups were matched for: age±5 years, gender, EF±5, peak VO2±3 (ml/min/kg) and recruiting center. Three hundred thirty-eight couples were found.
Results: 3447 patients (85% M; 61.5±11.8 yrs; EF 30.8±8.9%) were included in the study. In the entire population, CV death and cardiac transplantation occurred in 118 (21%) vs. 490 (17%) patients (p=0.026), while all-cause death was observed in 130 (23%) vs. 554 (19.2%) AF and SR patients, respectively, (p=0.039). Kaplan-Meier analysis showed worse prognosis of AF group for CV death + cardiac transplantation (p=0.045), while no differences were observed for any-cause death (p=0.065). In the matching analysis, CV death and cardiac transplantation occurred in 63 (18.6%) AF compared to 74 (21.9%) SR patients (p=0.293) and all-cause death in 71 (21%) AF compared to 80 (23.6%) events in SR patients (p=0.406). No survival differences between AF and SR patients were observed for both study outcomes. At multivariable Cox regression analysis, AF shows no independent predicitve role for both study outcomes in the overall population.
Conclusion: This large, multicenter study showed, by a 1:1 matching analysis, that AF is not independently associated to adverse outcome in HF and confirmed that AF is probably a marker of advanced disease, rather than a prognostic indicator, in patients with chronic, systolic HF.

P4885 | BEDSIDE

Clinical implication of the symptom onset in acute heart failure patients: a report from a cardiac care unit network emergency medical service database

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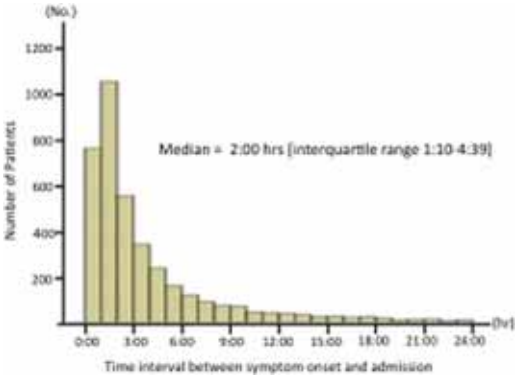
Background: Acute heart failure (AHF) is one of the frequently encountered conditions in the emergency department but little information is available in regards to the relationships between its timing, clinical background and outcomes.
Methods: A total of 3811 consecutive patients were admitted with AHF between 2009 and 2011 in 67 institutions in a Cardiac Care Unit Network, and registered to the on-going emergency medical service (EMS) registry. The symptom onset time was documented by the EMS team on-site and we divided the patients into two groups according to onset-to-admission (OTA) time. To define early vs. late responders to their AHF symptoms, median OTA time was used for the cutoff value. The primary outcome was all-cause mortality during hospitalization.
Results: The average age of registered AHF patients was 76.3±12.3 years, predominantly males (54.8%), and the average left ventricular ejection fraction was 43±16%. The median OTA time was two hours; between the early (≤2hr) and the late (>2hr) OTA group, the early group was in worse state of respiratory and neurological condition upon presentation, demonstrated by high respiratory rate, low oxygen saturation rate, and low neurological coma scale. Overall, 242 (6.5%) patients died during their hospitalization. Despite their worse clinical profile, shorter OTA time was associated with better in-hospital mortality after adjustment for known prognostic indicators (OR, 0.71; 95% CI, 0.52 to 0.97; P=0.034).



Distribution of onset-to-admission time.

Conclusion: Among patients with AHF, shorter OTA time was independently associated with better in-hospital mortality. Identification of the symptom onset may aid in triaging of the patients with AHF.

P4886 | BEDSIDE

Prognostic value of cardiac fibrosis in patients with non-ischemic cardiomyopathy without congestive heart failure: a multicentre magnetic resonance study

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Purpose: The aim of this prospective longitudinal study was to investigate the yet unknown clinical significance of myocardial fibrosis in non-ischemic cardiomyopathy (NICM) patients without history of congestive heart failure (CHF).
Methods: At 3 tertiary referral Centres, 228 NICM patients without CHF history were studied with cardiac magnetic resonance for late gadolinium enhancement (LGE) detection and quantification, and followed–up for a 23-month median period (interquartile range 13-37 months). The end-point was a composite of cardiac death, onset of CHF and aborted sudden cardiac death (SCD).
Results: LGE was detected in 61 (27%) patients. 31 (51%) patients with LGE reached the end-point, compared to 18 of 167 (11%) patients without LGE (HR: 5.104 [2.783-9.361], P<0.001). Patients with LGE had greater risk of developing CHF than patients without LGE (HR: 5.234 [2.609-10.500], P<0.001) and higher rate of aborted SCD (HR: 8.314 [1.664-41.548], P=0.010). Multivariate analysis showed that LGE was associated with high likelihood of composite end-point, independently of other prognostic determinants, including age, duration of disease and left ventricular (LV) volumes, mass and ejection-fraction (HR: 4.020 [2.082-7.762], P<0.001). Improvement chi-squared analysis disclosed that LGE addition to models including clinical data, alone or in combination with parameters of LV remodelling and function, yielded an improvement in outcome prediction (P<0.001). Addition of LGE to age and LV ejection-fraction improved risk stratification for composite end-point (net reclassification improvement [NRI]:29.6%) and onset of CHF (NRI: 25.4%, both P<0.001).

Conclusions: In NICM patients without CHF history, myocardial fibrosis is a strong and independent predictor of adverse outcome and improves risk stratification beyond clinical data and severity of LV systolic dysfunction.

P4887 | BEDSIDE
Risk factors for periodic breathing in heart failure patients with sleep apnea

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Purpose: The presence of periodic breathing (Cheyne-Stokes respiration, CSR) in patients with congestive heart failure (CHF) is associated with poor prognosis, regardless whether it occurs during day time or at night time during sleep. The aim of the present study was to determine the risk factors for night time CSR in a population of CHF patients with sleep apnea (SA).
Methods: The ongoing multi-center SchlaHF registry included prospectively 8341 CHF patients (New York Heart Association (NYHA) class ≥II and left-ventricular ejection fraction (LVEF) ≤45%) from cardiology practices and departments of hospitals. Patients were studied with a two-channel screening device (nasal airflow, pulse oximetry; ApneaLink, ResMed, Sydney, Australia) that detects CSR based on an algorithm using pattern recognition. Patients with suspected SA received full in-laboratory polysomnography with certified scoring.
Results: Of 1144 CHF patients with sleep apnea (Apnea-Hypopnea Index ≥15/hour of sleep) 784 (69%) had CSR. CHF patients with SA and CSR were significantly older (69±10 vs 65±11y), had lower LVEF (33±8 vs 36±8%) and arteriocapillary PaCO2 values (37.1±4.5 vs 38.8±4.8mmHg, $p<0.05$ for all comparisons) compared to those without CSR. In a multivariable regression model age (odds ratio, OR [95% confidence interval, CI]: 1.40 [1.22; 1.61] per 10 years) male gender (OR, [95% CI]: 2.01 [1.37; 2.93]), LVEF (OR, [95% CI]: 1.21 [1.11; 1.32] per 5% decrease), atrial fibrillation (OR, [95% CI]: 2.03 [1.47; 2.80]) and PaCO2 (OR, [95% CI]: 0.95 [0.92; 0.98]) were independent risk factors for CSR. Symptoms of CHF such as NYHA class≥III, nocturnal dyspnea and nocturia as well as body-mass index were not significantly associated with CSR.
Conclusion: In contrast to symptoms of CHF, age, male gender, impaired cardiac function, atrial fibrillation and low PaCO2 are independent risk factors for the occurrence of night-time CSR in CHF patients with SA.
Acknowledgement: This study was sponsored by ResMed Germany Inc.

P4888 | BEDSIDE
C-reactive protein and NT-proBNP for predicting mortality in patients with heart failure with preserved ejection fraction

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Aims: Heart failure (HF) with preserved ejection fraction (HFpEF) has a distinct pathophysiologic background but a mortality rate comparable to HF with reduced ejection fraction. Consequently, tailored risk prediction in these separate groups of HF is of major importance. Inflammation may play an important pathogenetic role in HFpEF due to its significant contribution to myocardial fibrosis. We therefore aimed to assess the predictive value of C-reactive protein (CRP) in patients with HFpEF with a particular focus on the prognostic gain in relation to N-terminal pro B-type natriuretic peptide (NT-proBNP).
Methods: CRP plasma levels were determined in 459 patients (age: 67.9 [60.6 - 73.3] years, 63.4% male) with HFpEF in the LUdwigshafen Risk and Cardiovascular Health (LURIC) study using a high-sensitivity assay. All patients were in a stable condition and diagnosis of HFpEF was based on current recommendations of the Heart Failure and Echocardiography Associations of the European Society of Cardiology.
Results: During a median follow-up of 9.7 years 40 percent (n=184) of these patients died. The corresponding 5-year mortality rate was 18% (n=82). CRP predicted all-cause mortality with an adjusted hazard ratio (HR) of 1.20 (95% CI: 1.02-1.40, P=0.018) and cardiovascular mortality with an adjusted HR of 1.32 (95% CI: 1.08-1.62, P=0.005) per increase of one standard deviation. Accordingly, stratification into tertiles of CRP showed a significant association with all-cause mortality with an adjusted HR of 1.83 (95% CI, P=1.23 - 2.72, P=0.002) for the third tertile compared to the first tertile and with cardiovascular mortality with an adjusted HR of 2.21 (95% CI: 1.33 - 3.66, P=0.002) for the third tertile compared to the first tertile. CRP was a significantly stronger mortality predictor in HFpEF patients than in a control group of 522 HF patients with reduced ejection fraction (for interaction, P=0.015). Furthermore, CRP added prognostic value to NT-proBNP: the lowest 5-year mortality rate of 6.8% was observed for patients in the lowest tertile of NT-proBNP as well as CRP. The mortality risk peaked in the group combining the highest values of NT-proBNP and CRP with a 5-year rate of 36.5%.
Conclusion: CRP turned out to be a strong, specific and independent predictor of mortality in HFpEF, but not in HFrEF, possibly pointing to immunologic processes with adverse impact on the course of HFpEF.

P4889 | BEDSIDE
Abnormal iron status is a key determinant of symptoms and submaximal exercise capacity in chronic heart failure patients

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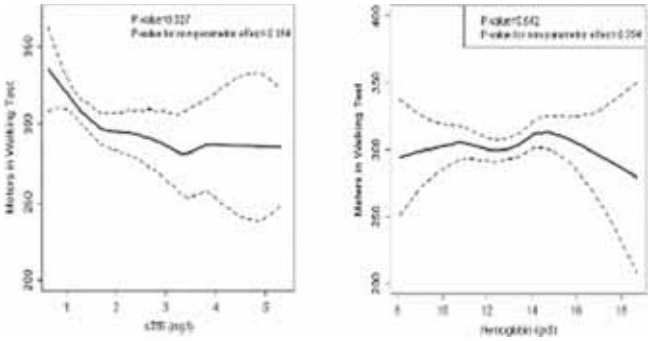
Purpose: Iron deficiency (ID) is associated with impaired peak VO2 exercise capacity, worse quality of life and poorer outcomes. The influence of impaired iron status on submaximal exercise capacity (SEC) has not been explored in chronic heart failure (CHF). This study was designed to evaluate the effect of ID and anaemia on SEC measured with the 6 minute walk test (6MWT) in CHF patients.
Methods: 538 consecutive CHF estable patients with either preserved or reduced LVEF were included. At inclusion, clinical variables were recorded and blood samples were obtained for evaluation of iron status. SEC was evaluated with the 6MWT. Symtoms presented during the test were also recorded. Anaemia was defined as haemoglobin <12 g/dL in women and <13 g/dL in men. ID was defined as ferritin<100 ng/mL or % transferrin saturation (TSAT) <20%. As additional marker of ID, the sTrF (serum soluble transferrin receptor) was evaluated.
Results: Baseline characteristics were: Mean age 71±11 years, 38% were female, 32% were in NYHA class III-IV, nearly half of the patients had preserved LVEF, 61% had ID and 45% had anaemia. In univariate unadjusted analysis, patients with ID had a reduced SEC compared to non-ID patients (291±104 meters vs 322±113, respectively; p=0.002). Symptoms during the test were more frequent in ID patients (35% vs 27%; p=0.028) and the most common symptom reported was fatigue. In adjusted multivariable analysis (GAM models, see figure), abnormal iron status but not Hb was significantly associated with impaired SEC.



Conclusion: In CHF ID but not anaemia is associated with impaired submaximal exercise capacity measured with 6MWT.

P4890 | BEDSIDE
Myocardial infarction, stroke or hospitalization for worsening heart failure: which event has the greatest prognostic significance in patients with heart failure?

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Background: The prognostic significance of worsening heart failure hospitalization (WHF) has never been compared to that of myocardial infarction (MI) or stroke in patients with chronic heart failure (HF).
Methods: We studied 4,128 patients with HF and preserved ejection fraction (HF-PEF) in the Irbesartan in Heart Failure with Preserved systolic function trial (I-Preserve; mean age 72 years; 60% women; mean follow-up 49.5 months) and 5,011 patients with HF and reduced ejection fraction (HF-REF) in the Controlled Rosuvastatin Multinational Trial in HF (CORONA; mean age 73 years; 24% women; median follow-up 32.8 months). Rates per 100 person-years (py) and hazard ratios (HR) for death were estimated for 0-30 days and ≥31 days after first WHF, MI or stroke hospitalization.
Results: 637 I-Preserve patients and 1,222 CORONA patients were hospitalized for WHF, MI (111 and 216, respectively) or stroke (147 and 163). Compared to patients with none of these events, 30-day mortality was higher in patients with each type of event (Table) and highest after MI or stroke compared with WHF

($p<0.01$ for both trials). However, the mortality risk beyond 30 days was similar for WHF, MI and stroke in both trials.

Mortality after event of worsening heart failure (WHF), myocardial infarction (MI) or stroke, in patients with HF-PEF (I-Preserve) or HF-REF (CORONA)

	No. of patients	Day 0–30			Day 31–		
		No. of deaths	Rate per 100 py	HR (95% CI)	No. of deaths	Rate per 100 py	HR (95% CI)
I-Preserve							
No. event	3,233	474	3	1.0 (ref)	474	3	1.0 (ref)
WHF	637	38	76	13.6 (9.3–19.9)	246	19	3.2 (2.7–3.9)
MI	111	21	268	51.4 (30.7–86.1)	27	15	3.1 (2.0–4.8)
Stroke	147	34	341	73.5 (49.7–108.9)	41	20	4.8 (3.4–6.1)
CORONA							
No. event	3,410	735	7	1.0 (ref)	735	7	1.0 (ref)
WHF	1,222	111	118	10.9 (8.6–13.9)	451	33	3.4 (2.9–4.0)
MI	216	38	259	24.8 (16.3–37.6)	68	32	4.1 (3.0–5.6)
Stroke	163	43	389	36.7 (24.4–55.2)	41	26	3.0 (2.1–4.4)

HR, hazard ratio.

Conclusion: Compared with WHF, MI and stroke are associated with a very high early mortality; thereafter all three events are associated with a similar increase in risk of death.

THROMBOSIS AND BLEEDING IN VALVE DISEASE

P4891 | BEDSIDE
Prosthetic valve thrombosis: about 159 patients

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Background: The prosthetic heart valve thrombosis (PVT) is a life threatening complication of mechanical valve prosthesis.
In the aortic and mitral position reported incidence varies from 0.5% to 6% per patient-year, and is highest in the mitral position and up to 20% in tricuspid valve prosthesis. Medical therapy has emerged as an alternative therapy in high-risk surgical patients, considering that surgical prosthetic valve replacement is related to significant operative morbidity and mortality rates.
Methods: From 2000 to 2013, 159 patients were hospitalized in our center for mechanical prosthetic valve thrombosis (PVT). The diagnosis of PVT was mainly assessed by echocardiography and/or fluoroscopy. There were 30 men and 129 women aged 15–75 years. Prosthetic valve location was mitral in 153 patients, tricuspid in 03 and aortic in 3. Predisposing causes of MVT were: poor compliance with warfarin, pregnancy or unknown.
The interval from first operation to PVT was from 1 day to 38 years. Delay from first symptoms to hospitalization ranged from 1 to 4 months.
Results: The diagnosis was an incidental finding (echocardiografic: increase in the transvalvular gradient); First clinical symptoms were: systemic emboli, progressive exertional dyspnea (NYHA II to III–IV), muffled opening or closing sounds of the prosthetic valve; left heart failure, stroke, and cardiogenic shock. Anticoagulation regimen was inadequate, recently stopped or incorrectly conducted. There were two groups; the first group (A) (114 patients) have been operated (CPB) and they prosthetic replacement was done (102) or declotting and excision of panus (12 patients). Medical therapy was established on first-line therapy for high-risk patients with mechanical valve thrombosis (second group (B)) (intravenous heparin, antivitamin K and aspirin) in patient without hemodynamic instability with success. Forty patients died after surgery (group A), the operative mortality was 12%. In group B, one patient was died (cerebral hemorrhage).
Conclusion: PVT remains a serious complication of mechanical heart valve prosthetic with high morbidity and mortality despite aggressive treatment by thrombolysis and/or surgery. Surgery treatment should be the preferred therapeutic modality for most patients with PVT. Thrombolysis, followed by heparin, warfarin, and aspirin, is advised in high-risk surgical candidates without hemodynamic instability under strict echocardiographic survey.

P4892 | BEDSIDE
Presentation, management and outcome of heparin induced thrombocytopenia after heart valve surgery - a single center experience

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Purpose: Use of unfractionated heparin (UFH) exposes patients to heparin-induced thrombocytopenia (HIT) which is a challenging issue both for diagnosis and patient management after heart surgery. In this study, we seek to describe the clinical and biological presentations, the management and the outcome of a large series of patients with a confirmed diagnosis of HIT in the setting of valvular heart surgery.
Methods: All patients who underwent valvular heart surgery at our institution from January 2007 to April 2013 were prospectively identified and included in a single-center registry. Clinical and biological data were screened in order to select patients with a confirmed diagnosis of HIT. Serologic testing for PF4-heparin antibodies and a platelet aggregation test were performed in all patients. The gold standard test for the diagnosis of HIT was the serotonin release assay. In-hospital and long-term outcomes were assessed.
Results: We identified 100 patients during this 76-month period. Mean age was 63±16 years, 48% of female patients. Aortic valve replacement was performed in 72 cases, mitral valve replacement in 31 cases, tricuspid valve replacement in 1 case and mitral valve plasty in 10 cases. The mean time to diagnosis from surgery was 9±3 days. A majority of patients (83) were asymptomatic with only isolated thrombocytopenia at the time of diagnosis. A fall in platelet count >50% was observed in 67 cases. In-hospital diagnosis circumstances or complications were arteriovenous thromboembolic events reported in 10 cases (6 cases of acute ischemic stroke), left atrial thrombus in 7 cases, prosthetic valve thrombosis in 10 patients including 1 case of valve obstruction, dermatologic manifestations in 3 cases. UFH was immediately stopped in all cases followed by the introduction of danaparoid sodium (97). Anti-aggregation therapy was associated in 6 cases. No thrombolytic therapy, interventional radiology procedure, secondary surgery, intravenous immunoglobulin or plasmapheresis were performed. Mean follow-up time was 38 months during which only 4 patients died (cardiac death=1) including 1 death<30 days. Recurrence of thromboembolic events were seen in only 5 cases following hospital discharge.
Conclusions: To our knowledge this is the largest series of patients with a confirmed diagnosis of HIT occurring in the setting of valvular heart surgery. The incidence of HIT was low as well as the proportion of thromboembolic events. Persistent thrombocytopenia was the most frequent presentation. Early diagnosis and prompt treatment are associated with good in-hospital and long-term outcomes.

P4893 | SPOTLIGHT
The role of anti-tpa antibodies in patients with prosthetic heart valve thrombus thrombolysed with recombinant tissue-type plasminogen activator

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Purpose: Thrombolytic therapy (TT) is effective for the treatment of prosthetic heart valve thrombosis (PHVT). Due to its high fibrin specificity recombinant tissue-type plasminogen activator (rt-PA) is widely used in the management of PHVT. Infusion of rt-PA may induce the production of antibodies. In this study, we aimed to evaluate the relationship between anti-tPA antibody (ATA) levels and presence of thrombus (THR), responsiveness to TT with rt-PA and development of rethrombosis in patients with prosthetic heart valves.
Methods: The study is designed as double blind fashion in 2 centers (Turkey,Italy). In order to detect ATA, plasma samples were collected from 28 PHVT patients at baseline and then 15, 30,45, 90 and 180 days after TT and from 31 controls at baseline only. ATA levels were assayed in human plasma by an enzyme-linked immunosorbent assay that uses rt-PA for capture and mouse monoclonal anti-human immunoglobulin G (IgG) or M (IgM) followed by peroxidase-conjugated anti-mouse immunoglobulin antibodies for detection.
Results: There was a significant difference in median levels of ATA between the PHVT patients before TT and controls in terms of IgM and IgG (17.88±24.7 vs 3.33±3.48, p:0.005 for IgG and 30.32±22.97 vs 15.78±14.03, p:0.01 for IgM). IgM levels peaked 15 days and IgG levels peaked one month after rt-PA infusion. TT failed in 6 patients (21%) and rethrombosis occured in 9 patients (32%). In failed TT group baseline IgM levels were significantly higher compared to successful TT group (50.46±34.58 vs 24.28±14.59, p=0.023). In rethrombosis group baseline IgG levels were significantly higher than the remaining PHVT patients (30.20±32.79 vs 8.01±12.01, p=0.019). Baseline IgG level of >3,7 yielded an area under the curve value of 0.780 (95% confidence interval 0.597 to 0.963, sensitivity 80%, specificity 60%, $p<0.02$) for rethrombosis and baseline IgM level of >34,2 yielded an area under the curve value of 0.808 (95% confidence interval 0.643 to 0.974, sensitivity 83%, specificity 75%, $p<0.024$) for failed TT. Also there was a moderate positive correlation between the baseline IgM levels and the dose of rt-PA (r=0.466, p=0.038) in successful TT group.
Conclusion: Native ATA may act in vivo as inhibitors of rt-PA function. Patients with abnormally high levels of ATA may have an additional risk for THR formation, responsiveness to TT with rt-PA and development of rethrombosis. Furthermore, the infusion of rt-PA may trigger the production of specific antibodies that bind to rt-PA, thus potentially may reduce its function and may participate in the hypofibrinolytic status.

P4894 | BEDSIDE

Impact of pre- and post-procedural anemia on incidence of acute kidney injury and 1-year mortality after transcatheter aortic valve implantation. Insights from the FRANCE 2 Registry

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Background: Among patients with cardiovascular disease, anemia and renal insufficiency have been reported to influence each other negatively. However, how anemia affects the renal function and outcomes after TAVI has not been adequately elucidated. Thus, the aim of this study is to evaluate the influence of pre- and post-procedural anemia on the incidence of renal insufficiency, especially AKI, and outcomes in patients undergoing TAVI.
Methods and results: Data from the French national TAVI registry were collected for 3,472 patients who underwent TAVI between January 2010 and December 2012. Of 3,472 patients, 2,137 were in the no/mild anemia group, 748 were in the moderate anemia group, and 587 were in the severe anemia group before TAVI. Increased anemia severity before TAVI was associated with significantly different rates of 1-year mortality (15%, 19% and 24%, $p<0.01$). The incidence of AKI was significantly higher in the moderate and severe anemia groups (5%, 8% and 10%, $p<0.01$). Furthermore, we divided 3,472 patients into 3 groups according to post-procedural anemia, as measured by a drop in hemoglobin (Hb) levels after a procedure: <2 g/dl (n=1633, group 1), 2 to <4 g/dl (n=1458, group 2), and >4 g/dl (n=381, group 3). Higher rate of Hb drop was associated with significantly different rates of 1-year mortality (16%, 18% and 23%, $p<0.01$), with similar differences in the incidence of AKI (6%, 7% and 10%, p=0.04). After adjustment for considerable influential confounders in logistic regression multivariate model, both pre-procedural anemia and post-procedural Hb drop were associated with an increased risk of the incidence of AKI (OR 1.74, 95%CI: 1.43-2.12, $p<0.01$; HR 1.81, 95%CI: 1.44-2.28, $p<0.01$, respectively). After adjustment for considerable influential confounders in COX-regression multivariate model, both pre-procedural anemia and post-procedural Hb drop were associated with an increased risk of 1-year mortality (HR 1.38, 95%CI: 1.23-1.56, $p<0.01$; HR 1.45, 95%CI: 1.26-1.67, $p<0.01$, respectively).
Conclusions: Both pre- and post-procedural anemia was significantly associated with the incidence of AKI and 1-year mortality.

P4895 | BENCH

In-vitro comparison of danaparoid, unfractionated heparin and enoxaparin in preventing thrombus formation on mechanical heart valves

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Purpose: Periprocedural switching from oral to parenteral anticoagulants in patients after mechanical heart valve replacement is challenging, especially in patients additionally suffering from HIT (heparin-induced thrombocytopenia).
This in-vitro study aimed to investigate whether danaparoid – a heparinoid approved for the prophylaxis and treatment of thromboembolic disorders in patients suffering from HIT- is as efficacious as unfractionated heparin and enoxaparin in preventing thrombus formation on mechanical heart valves.
Methods: Blood samples (250 ml) from healthy male volunteers were treated with either UFH 0.9 IU/ml, enoxaparin 0.6 IU/ml, or danaparoid 0.8 IU/ml (n=10, each). Bileaflet mechanical heart valves were placed in an in-vitro device (THIAII, Thrombotester) allowing exposure to anticoagulated blood samples under pulsatile circulation conditions at 60 beats per minute for a total exposure time of 60 min.
Heart valve thrombus weight, coagulation parameters and electron microscopic evaluation with regard to platelet, erythrocyte and fibrin deposition on the leaflet surfacewere defined as endpoints.
Results: Levels of anticoagulation were proven to be at therapeutic range by measuring activated clotting times (ACT) for UFH, and mean anti-FXa-activities for enoxaparin (n-hep assay) and danaparoid treatment (orgaran assay).
Overall thrombus weight was significantly reduced by danaparoid treatment (0.002±0.001 g) as compared to UFH (0.153±0.126 g) and enoxaparin (0.295±0.181 g) treatment (one-way ANOVA-analysis: $p<0.001$). Furthermore, enoxaparin treatment resulted in significantly increased thrombus weights as compared to UFH application (p=0.019).
Results from electron microscopy showed no significant differences between danaparoid, UFH and enoxaparin groups regarding the deposition of erythrocytes (p=0.096).
Platelet deposition was significantly reduced by danaparoid compared to UFH and enoxaparin ($p<0.001$). While danaparoid treatment was as efficacious in preventing fibrin deposition as UFH ($p>0.05$), application of danaparoid even significantly reduced fibrin formation as compared to enoxaparin (p=0.004).
Conclusion: In summary, danaparoid proved to be at least as effective as UFH and enoxaparin in preventing in-vitro thrombus formation on mechanical heart valves. These favorable results suggest that danaparoid may constitute a potent alternative for patients with mechanical heart valve replacement in need of periprocedural parenteral anticoagulation in the case of HIT.

P4896 | BEDSIDE

Bleeding vs. ischemia: finding a balance in antithrombotic therapy following transcatheter aortic valve implantation - a meta-analysis

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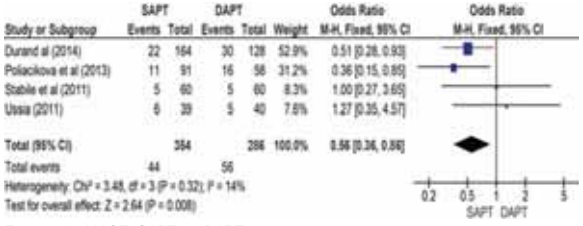
Purpose: Despite the clinical benefits of transcatheter aortic valve implantation (TAVI), the reported risk of stroke and bleeding events is exceedingly higher compared to other cardiac interventions. Dual antiplatelet therapy (DAPT) with clopidogrel and aspirin is recommended by the guidelines, but limited evidence is available to support decision making in antiplatelet therapy.
Methods: Pubmed, MEDLINE, EMBASE and Central (2002-2014) were searched for English studies that compared DAPT with single antiplatelet treatment (SAPT) following TAVI. Primary endpoint was the combined endpoint of major adverse cardiac and ischemic cerebrovascular events (MACE) at one month, including both ischemic as bleeding events. Secondary endpoints were stroke and major bleeding.
Results: In total 4 studies were eligible (Figure 1). Overall MACE occurred significantly less in patients treated with SAPT than with DAPT (OR 0.56, 95% CI 0.36 to 0.86; P=0.008). No clear benefit of DAPT in comparison to SAPT was observed in preventing stroke occurrence 30 days post-TAVI (OR 0.95, 95% CI 0.32-2.84, P=0.89). DAPT was associated with an increased occurrence of major bleeding (OR 0.32, 95% CI 0.17-0.60, P=0.38).



Forrest plot MACE: SAPT vs. DAPT.

Conclusion: Treatment with SAPT one month following TAVI was associated with a decreased occurrence of MACE and major bleeding without increasing the risk of future stroke, indicating a better risk/benefit ratio in comparison to DAPT.

P4897 | BEDSIDE

Unexpected high incidence of obstructive thrombosis in porcine bioprostheses in aortic valve position

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Obstructive thrombosis of bioprosthetic valves has been considered to be rare with an incidence of <1%. However, recently considerably higher rates have been reported with a frequent necessity of reoperation.
Patients and methods: All patients who received a single stented bioprosthetic valve in the aortic position at our institution between 2007 and 2012 were included in the analysis. We investigated clinical, procedural, and follow-up data with the aim to identify the incidence, potential risk-factors and clinical course of patients with obstructive valve thrombosis in aortic position.
Results: 1751 patients (75±9 years) required a single stented aortic bioprosthetic valve, 29% in combination with bypass surgery. Four types of pericardial prostheses were implanted in 1003 patients and two types of porcine prosthesis in 748 patients. Sixteen patients with obstructive thrombosis were identified in porcine valve prosthesis (2.1%) 354±253 days postoperatively, whereas none was observed in pericardial valves ($p<0.001$). Two unstable patients (12%) required reoperation; the remaining fourteen could be successfully treated with phenprocoumon. Risk for obstructive thrombosis was 44 times higher [95%CI 2.7-736] in porcine compared to pericardial prosthesis. The presence of a porcine bioprosthesis was identified as a strong and independent predictor of obstructive thrombosis in a multivariate model including clinical, procedural and postoperative echocardiographic parameters.
Conclusion: Obstructive thrombosis of stented bioprostheses in the aortic valve position seems to be restricted to porcine valves and occurs in about 2% of the patients with this type of prosthesis.

CHEST PAIN ASSESSMENT IN THE EMERGENCY DEPARTMENT

P4898 | BEDSIDE
Heart rate at admission is a predictor of in-hospital mortality in patients with acute coronary syndromes - results from 58 European hospitals - the EURHOBOP study

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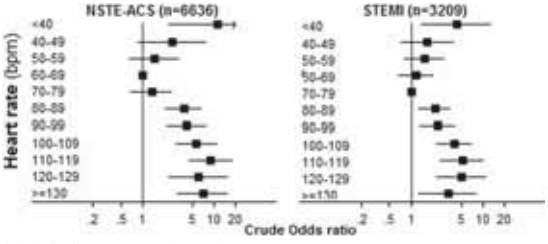
Purpose: Heart rate is a fundamental clinical parameter and may have prognostic importance in the acute setting. Heart rate at admission and in-hospital mortality in patients with acute coronary syndromes (ACS) was investigated.
Methods: Consecutive ACS patients admitted 2008-2010 across 58 hospitals in six participant countries of the EURHOBOP collaboration (Finland, France, Germany, Greece, Portugal and Spain). Associations between heart rate at admission and in-hospital mortality were estimated by logistic regression models adjusting for cardiovascular risk factors, including known heart failure, kidney disease, previous stroke, and ischemic heart disease. Cardiogenic shock patients were excluded.
Results: A total of 10374 patients were included; 6636 with non-ST-elevation ACS (NSTE-ACS) and 3209 with ST-elevation myocardial infarction (STEMI).
For both NSTE-ACS and STEMI patients a U-shaped relationship between admission heart rate and mortality was found (Figure).
For NSTE-ACS, an admission heart rate of 60-69 was associated with the lowest risk; a heart rate <40 bpm was associated with a 11-fold increased risk and heart rate categories above 80 bpm with a 3.8 to 8.8-fold increased risk of mortality. The relationship persisted in the multivariable models.
For STEMI patients, heart rates between 70-79 bpm were associated with the lowest risk, and a heart rate <40 bpm was associated with a 4.3-fold increased risk and above 80 bpm with 2.2 to 5.3- fold increased risk of mortality (Figure). In the adjusted model heart rates above 80 bpm remained associated with increased risk.



Admission heart rate and mortality.

Conclusion: Heart rate at admission is a very powerful predictor of in-hospital mortality in patients with ACS. ACS patients with admission heart rate above 80 bpm or bradycardia should receive particular attention.

P4899 | BENCH
A novel electrocardiographic biomarker for prediction of intrahospital mortality in the medical emergency department

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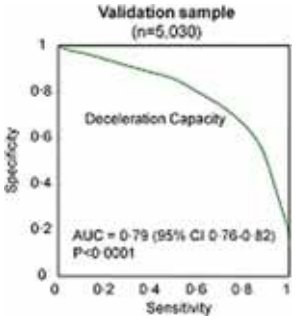
Purpose: Cardiac autonomic function may yield important prognostic information in emergency patients but is currently not used for clincial decision making. Here, we propose a novel electrocardiographic marker for automated short-term assessment of cardiac autonomic function.
Methods: The method was developed in 700 patients admitted to the medical emergency department (ED) of a large university hospital (training sample) and validated in 5,030 patients (validation sample). Cardiac autonomic function was assessed by means of a modified version of deceleration capacity (DC) of heart rate from routine monitors within the first minutes after ED admission. The developed algorithm allows a fully automatic DC assessment without manual intervention. Primary endpoint was intrahospital and 10-day mortality. Multivariate analysis included physiological parameters (heart rate, arterial blood pressure, respiratory rate, temperature and oxygenation), the APACHE II score as well as biochemical markers (sensitive troponins, C-reactive protein, glomerular filtration rate).
Results: In the validation sample, 135 of the 5,030 patients reached the primary endpoint. DC was significantly lower in non-survivors than survivors (2.9±2.0 ms vs. 5.6±3.0 ms, p<0.0001). The area under the receiver-operator characteristics curve was 0.789 (95% CI 0.760-0.817, p<0.001; Figure). DC >7ms (cut-off derived from the training sample) yielded a negative predictive value of 99.6% at a sensitivity level of 94.8%. Multivariate analyses revealed that the predictive value of DC was independent from physiological parameters, the APACHE II score and biochemical markers.



ROC curve (primary EP).

Conclusions: DC is a strong and independent predictor of short-term mortality among unselected patients of a medical ED that rapidly identifies low risk patients.

P4900 | SPOTLIGHT
Efficacy of nurse-led chest pain assessment within the emergency department

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Our heart centre provides 24/7 Acute Coronary Syndrome (ACS) services including Primary Percutaneous Coronary Angioplasty (PPCI) for a population of approximately 850K people. To support our services we have developed a team of nurse practitioners (NP's) who undertake roles that have been historically delivered by medical staffs for example: first contact in the Emergency Department (ED) and chest pain/ arrhythmia and heart failure clinics. The advantage of NP's is that once trained the department has a cohort of "middle grade" equivalent staff who are able to deliver sustainable robust services with an focus on evidenced based practice and individualised patient care that are less subject to whims of the labour market and training rotations. This paper discusses our experience in developing this service and how our service could be replicated in other institutions. In the past 2-years the NP's have reviewed n=5,496 "all comer" chest pain patients in the ED. Of this cohort 58% were discharged within the UK target of 4-hours. Of the admitted patients, 58% were diagnosed as having ACS by a consultant cardiologist. We undertook a retrospective randomised audit of the same patient population who had been seen by ED "middle grade" (registrars and associate specialists)doctors for comparison. Data showed the NP's were less likely to admit (42% vs. 82%) and were more likely to correctly identity ischemic patients (58% vs. 5%) when the differential diagnosis was confirmed by a consultant cardiologist. A concern raised was that the NP's were "over discharging" inappropriate patients. N=2,673 patients were followed up for 30-days post discharge. Of this cohort there were no unexpected deaths and 0.19% re-attended our ED with a confirmed ACS. This data compares favourably with published trial and registry data. Patient Reported Outcome Measures (PROMS) consistently show high patient satisfaction with the service and the quality of care provided.
To conclude, appropriate trained NP's can provide safe, robust and patient centred chest pain services in the ED and offer a practical alternative to locum/ staff grade doctors in service delivery in acute cardiac care.

P4901 | BEDSIDE
Comparison of exercise electrocardiography and exercise echocardiography for the prediction of outcome in patients referred to a chest pain unit

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Purpose: To assess the relative value of exercise electrocardiography (ExECG) and exercise echocardiography (ExEcho) for predicting outcome in patients referred to a chest pain unit for acute chest pain, nondiagnostic electrocardiograms (ECGs) and negative troponin levels.
Methods: ExECG and ExEcho were performed in parallel in 1172 patients with non-traumatic acute chest pain suspected of having an ischemic origin, who had nondiagnostic but interpretable baseline ECGs and negative troponin levels. Patients with repolarization abnormalities precluding a proper interpretation of ExECG were not included. A positive ExECG was defined as the development of ST-segment deviation of ≥1 mm which was horizontal or sloping away from the isoelectric line 80 ms after the J point. A positive ExEcho was defined as the demonstration of echocardiographic ischemia, i.e., the appearance of new or worsening wall motion abnormalities with exercise. The tests were considered negative in the absence of exercise-induced abnormalities at ≥85% of maximum age-predicted heart rate. Otherwise, the tests were considered inconclusive. The

primary endpoint was a composite of cardiac death, nonfatal myocardial infarction or coronary revascularization at 6 months.
Results: The primary endpoint occurred in 4/680 patients (0.6%) with both negative ExECG and ExEcho, 4/66 patients (6.1%) with positive ExECG and negative ExEcho, 69/160 patients (43.1%) with negative ExECG and positive ExEcho, 110/167 patients (65.9%) with both positive ExECG and ExEcho, and 8/119 patients (6.7%) with inconclusive results. The C-index for predicting the primary endpoint of a model based on clinical and resting echocardiographic data (sex, age, cardiovascular risk factors, history of myocardial infarction, prior coronary revascularization, typical angina and resting left ventricular ejection fraction) was 0.679. The sequential addition of ExECG data (exercise-induced chest pain, ischemic ECG changes, exercise workload and rate pressure-product) and ExEcho data (echocardiographic ischemia) significantly increased the C-statistic of the model to 0.876 and 0.942, respectively ($p<0.001$ for both steps).
Conclusion: ExEcho provides significant incremental prognostic information for the prediction of cardiac events over clinical, resting echocardiographic and ExECG data in patients referred to a chest pain unit for acute chest pain, nondiagnostic ECGs and normal troponin levels.

P4902 | BENCH
Frequency and prognosis of unstable angina pectoris in the era of the universal definition: a clinical cohort study

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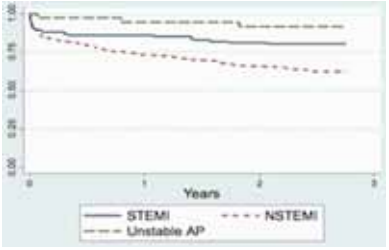
Purpose: To assess the frequency and prognosis of pts with unstable angina pectoris (UAP) in the era of the universal definition of myocardial infarction (MI).
Methods: During a one-year period we prospectively studied unselected pts admitted to a university hospital. All pts having troponin I (cTnI) measured because of a suspected acute coronary syndrome were included. cTnI was analyzed on an Architect c16000, and a value >30 ng/L was considered the decision limit for the diagnosis of a myocardial infarction (MI). UAP was defined as unstable chest discomfort (rest, new onset, or worsening of angina) and dynamic ECG changes. In UAP pts cTnI was ≤30 ng/L. The MI diagnosis was according to the universal definition, and pts were classified as ST-elevation MI (STEMI) or non-ST-elevation MI (NSTEMI). Follow-up was at least one year with all-cause mortality as the clinical end-point.
Results: From January 2010 to January 2011 a total of 3762 pts were considered. 516 pts had acute coronary syndrome. UAP was present in 37 (7%), STEMI in 133 (26%), and NSTEMI in 346 pts (67%). The mean age (±SD) differed significantly between the three subgroups: UAP 66±13, STEMI 68±14 and NSTEMI 72±13 yrs ($p=0.0005$). During a median follow-up of 2.1 years 153 pts died, and the mortality rates were: UAP 8%, STEMI 20%, and NSTEMI 36% ($p<0.0001$; figure).



Survival rate in acute coronary syndrome.

Conclusion: In the second decade of the new millenium UAP is present in less than 10% of pts with acute coronary syndrome. The long-term prognosis in these UAP pts appears to have improved with an annual mortality rate of 4%. The reason for the reduced UAP frequency is most likely multifactorial including the advent of more sensitive troponin assays and the introduction of the universal definition of MI.

P4903 | BEDSIDE
New left bundle branch block and acute myocardial infarction revisited: insights from a multicentre diagnostic study

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Purpose: Current ESC guidelines recommend early revascularization therapy in patients with new or presumably new complete left bundle branch block (nLBBB) and suspected acute myocardial infarction (AMI). However, these recommendations are largely based on data from outdated fibrinolytic trials. The aim of our study was to investigate on the incidence of nLBBB in patients presenting with suspected AMI and the predictive value of nLBBB for AMI.
Methods: 2938 unselected patients presenting with acute chest pain on the emergency department were included in a prospective multicentre diagnostic study. In case of the presence of a LBBB on a previous ECG a LBBB was considered as being old (oLBBB) otherwise it was classified as being new or presumably new (nLBBB). The final diagnosis was adjudicated by two independent cardiologists.
Results: 84 (2.9%) patients had a LBBB at presentation of whom 29 (35%) were considered as being new or presumably new (nLBBB). AMI was the final diagnosis in 13 (45%) patients with nLBBB compared to 20 (37%) with oLBBB ($p=0.5$) and 570 (20%) without a LBBB ($p<0.001$). While nLBBB was associated with an adjudicated diagnosis of AMI (OR 3.19, $p=0.002$ versus OR 2.32 for oLBBB, $p=0.003$), the positive predictive value of nLBBB for AMI was only 45%. Moreover, when corrected for age and gender, nLBBB and oLBBB no longer were significant predictors of AMI.
Conclusion: Less than half of patients with nLBBB presenting with suspected AMI will ultimately be found to have AMI. These findings raise concern about the recommendation to consider nLBBB as a STEMI equivalent regarding the need for immediate coronary angiography in current ESC guidelines.

P4904 | BEDSIDE
Optimal cutoff-values of roche high-sensitivity cardiac troponin T in patients with kidney disease for the early diagnosis of acute myocardial infarction

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Purpose: The recent introduction of more sensitive cardiac troponin assays improved the early diagnosis of acute myocardial infarction (AMI). However, its diagnostic utility has never been tested in patients with kidney disease (KD), who are known to have elevated levels of cardiac troponins (cTn) already in the absence of AMI, which may lead to a lower diagnostic value of more sensitive cTn in this high-risk subgroup.
Methods: We conducted an international multicenter study to examine the diagnostic accuracy of the Roche high-sensitivity (hs) cTnT assays in 2813 consecutive patients presenting to the emergency department with symptoms suggestive of AMI, of whom 447 (16%) were determined to have KD (MDRD GFR $<60 ml/min/1.73m^2$) and to derive the optimal cutoff value for the diagnosis of AMI in patients with KD. The diagnostic accuracy was further compared to a standard cTn assay (Roche Troponin T fourth generation). The final diagnosis was adjudicated by two independent cardiologists based on hs-cTnT using all available data.
Results: AMI was the final diagnosis in 36% (n=160) of all KD-patients as compared to 18% in patients with normal kidney function ($p<0.001$). Among KD-patients with other diagnoses than AMI, baseline hs-cTnT-levels were elevated above the 99thpercentile in 68%, In patients with KD the diagnostic accuracy at presentation, quantified by the area under the receiver-operator-characteristic curve (AUC), was significantly greater for hs-cTnT as compared to the standard assay (AUC for hs-TnT, 0.87 vs. AUC for the standard assay, 0.82, $p=0.001$). In patients presenting within three hours after the onset of chest pain, hs-cTnT remained superior compared to the conventional cTnT (AUC 0.82 vs. 0.72, $p=0.001$). In KD, the optimal hs-cTnT cutoff derived from the ROC curve was 29.5 ng/l compared to 16 ng/l in patients with normal kidney function (official 99th percentile cutoff-value 14 ng/l).
Conclusions: The investigated hs-cTnT assay has a high diagnostic accuracy also in KD-patients and is superior to conventional cTn-assays. Mild elevations are common in non-AMI patients. However, the test-specific optimal cutoff-level in KD-patients seems to be nearly twice as high as the standard 99th percentile level.
ClinicalTrials.gov number, NCT00470587

FRACTIONAL FLOW RESERVE: OBJECTIVE MEASUREMENT

P4905 | BEDSIDE
The resistance in the coronary microvasculature substantially impacts the assessment of epicardial stenosis severity by fractional flow reserve

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Purpose: Fractional flow reserve (FFR) is purportedly dictated by the extent of epicardial disease, but the involvement of the coronary microvasculature may be obscure the assessment of epicardial disease by means of FFR. We documented the impact of hyperaemic microvascular resistance (HMR) on the relationship between FFR and the physiological epicardial disease severity as assessed by the hyperaemic stenosis resistance index (HSR).
Methods and results: We studied 299 target vessels with intracoronary pressure and flow measurements to determine FFR, HSR, and HMR. In 178 patients, HMR was also measured in a reference coronary artery. A total of 44 target vessels with $FFR<0.6$ were excluded because of the potential neglection of collateral flow

contribution. In the 255 remaining target vessels, target vessel HMR was stratified in a low, intermediate, and high HMR group according to reference vessel HMR tertiles.

The magnitude of HMR modulated the relationship between FFR and HSR, illustrated by the difference in regression slopes across the HMR groups (-1.99 (95% CI: -2.21 to -1.78), -2.84 (95% CI: -2.97 to -2.71), and -5.39 (95% CI: -6.04 to -4.74) for low, intermediate, and high HMR, respectively; overall $p<0.001$). For a given stenosis severity, characterized by a narrow range of HSR, FFR increased with increasing HMR (Fig. 1). The correlation between FFR and HSR (r2=0.54, $p<0.001$) improved substantially after adjustment for HMR (HMR-adjusted partial correlation r2=0.73, $p<0.001$).

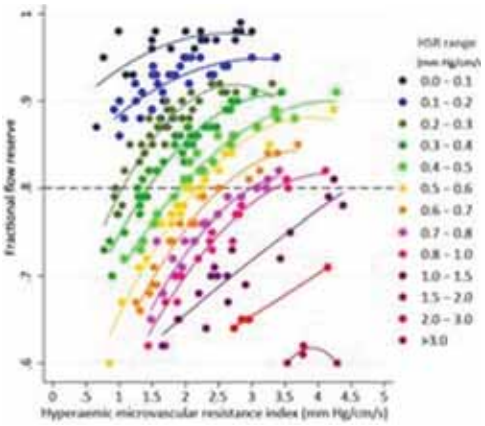

Figure 1

Conclusions: Identification of epicardial disease severity by FFR is obscured by the magnitude of coronary microvascular resistance. Appropriate interpretation of FFR requires information on microvascular status, which illustrates the necessity of combined pressure and flow measurements in daily practice.

P4906 | BEDSIDE
Correspondence of Invasive FFR vs. perfusion MRI at 3tesla in patients with recent NSTEMI

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Background: Coronary microcirculatory function may be disturbed in patients with a recent acute coronary syndrome. Fractional flow reserve (FFR) is an index of coronary stenosis severity validated in patients with stable symptoms. We aimed to assess the diagnostic accuracy of FFR in patients with a recent non-ST segment myocardial infarction (NSTEMI) when compared with 3T stress perfusion MRI.

Methods: 106 patients with NSTEMI referred for early invasive were included. FFR was measured in all major patent epicardial coronary arteries with a visual stenosis estimated at ≥30%. In addition, where clinically appropriate, an FFR assessment following PCI was also performed. Myocardial perfusion was assessed non-invasively with stress MRI at 3T. MRI provided the reference dataset. Hyperaemia for FFR and MRI was established with intravenous adenosine (140 μg/kg/min). In a small number of patients MRI was performed prior to coronary angiography/PCI. The stress and rest perfusion scans were viewed simultaneously, and areas of hypoperfusion were assigned to coronary territories using the AHA coronary arterial segment model. Coronary artery territories with abnormal perfusion were recorded. Disagreement between observers were adjudicated by a third blinded observer. The MRI analyses were performed blind to the FFR results.

Results: Mean age was 56.7±9.8 years and 82.6% male. Mean time from FFR evaluation to MRI was 5.8±3.1 days. Mean infarct size was 5.4±7.1% of left ventricular volume and mean troponin was 5.2±9.2mg/L. 1696 segments were available for analysis. 34 segments were excluded from the analysis due to problematic image quality. 824 segments were available for comparison with FFR. 176 vessels were assessed – 104 in the infarct-related arteries and 72 in the non-infarct-related arteries. There was a negative correlation between the number of segments and FFR ($r = -0.79$, $0<0.0001$).

The sensitivity, specificity, PPV and NPV for FFR≤0.8 was 91.17%, 95.7%, 91.2% and 95.7% respectively. The sensitivity, specificity, PPV and NPV for FFR≤0.75 was 82.35%, 98.5%. 96.5%, and 93.2% respectively.

ROC analysis demonstrated that the optimal cut off value of FFR for demonstrating reversible perfusion abnormalities on MRI was ≤0.8 (AUC 0.93 (0.88-0.99), $p<0.0001$). This was associated with a sensitivity of 91.2% and a specificity of 99.5%.

Conclusion: FFR measured invasively in patients with recent NSTEMI corresponds well with stress perfusion MRI at 3T.

P4907 | BEDSIDE
The ischaemia-inducing potential of FFR-positive coronary stenosis of intermediate severity is dictated by the combination of epicardial and microvascular resistance

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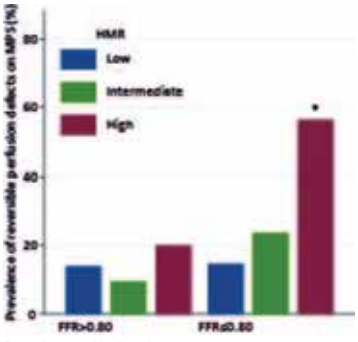
Purpose: Fractional flow reserve (FFR) is considered to be a stenosis-specific index. However, microvascular disease contributes to the occurrence of myocardial ischaemia, and FFR values may be obscured by such microvascular involvement. We documented the impact of hyperaemic microvascular resistance (HMR) and hyperaemic stenosis resistance (HSR) on the FFR-guided identification of inducible myocardial ischaemia.

Methods: We assessed 299 target vessels by means of intracoronary pressure and flow measurements to determine FFR, HSR, and HMR. Myocardial perfusion scintigraphy (MPS) was used to identify inducible myocardial ischaemia. In 178 patients, HMR was also measured in a reference coronary artery. A total of 44 vessels with FFR<0.6 were excluded because of the potential neglection of collateral flow contribution. In the remaining 255 target vessels, HMR was stratified in a low, intermediate, and high HMR group according to reference vessel HMR tertiles.

Results: Among 111 stenoses with a positive FFR (≤0.80), FFR was equivalent across the HMR groups: median FFR was 0.74 (0.69–0.78), 0.74 (0.70–0.77), and 0.73 (0.69–0.78) for low, intermediate, and high HMR, respectively (p=0.94). Despite equivalent FFR across groups, the prevalence of ischaemia was significantly higher when HMR was high (Figure: *$p<0.05$ for all comparisons), which was paralleled by a concomitant significant increase in HSR: median HSR was 0.44 (0.34 – 0.61), 0.70 (0.57 – 0.81), and 1.04 (0.80 – 1.50) for low, intermediate, and high HMR, respectively ($p<0.001$).



Prevalence of ischemia

Conclusion: The ischaemia-generating potential of FFR-positive stenoses is dictated by the extent of epicardial and microvascular resistance to coronary blood flow, which may not be adequately reflected in the stenosis significance as assessed by FFR.

P4908 | BEDSIDE
Coronary flow velocity reserve is an independent predictor of 10-year major adverse cardiac events after deferral of revascularization in patients with stable coronary artery disease

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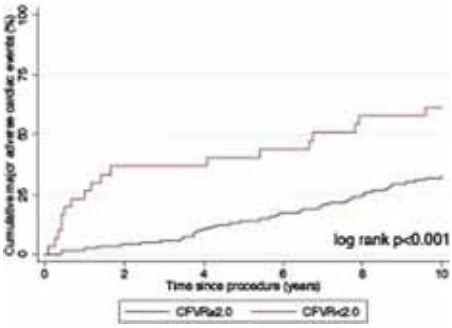
Purpose: Coronary flow velocity reserve (CFVR) is a combined marker of epicardial and microvascular disease. As microvascular involvement in ischemic heart disease is increasingly recognized as a contributor to adverse outcome, CFVR may provide additional prognostic information over specific markers of epicardial disease, such as hyperemic stenosis resistance (HSR) or fractional flow reserve (FFR). Therefore, we evaluated the independent prognostic value of CFVR for long-term clinical outcome after deferral of revascularization.

Methods: Between April 1997 and September 2006, revascularization was deferred in 157 patients with 186 intermediate stenoses studied with intracoronary pressure and flow measurements. CFVR<2.0 was considered abnormal. In the presence of multi-vessel disease, one of the vessels was randomly selected for subsequent analyses. Ten-year major adverse cardiac event rates ((MACE) composite of cardiac death, myocardial infarction, and target vessel revascularization) were estimated with the Kaplan Meier method, and compared with the log rank test. The independent prognostic value of CFVR for long-term MACE was assessed by multivariate Cox regression.

Results: Median follow-up was 11.7 years (Q1, Q3: 9.9, 13.3). CFVR <2.0 was associated with significantly higher 10-year MACE (32.9% vs. 63.1%, $p<0.001$;

Figure). After adjustment for age, aspirin use, ACE-inhibitor use, and HSR, decreasing CFVR was associated with a 1.8-fold increase in MACE hazard per CFVR unit (95% confidence interval: 1.1 – 2.8, p=0.01). Results were equivalent after adjustment for FFR (Hazard ratio 1.9, 95% CI: 1.2 – 3.0, p=0.01).



Kaplan-Meier curves.

Conclusion: Low CFVR is associated with adverse long-term clinical outcome after deferral of revascularization, independent of epicardial disease severity as assessed by HSR or FFR.

P4909 | BEDSIDE
Doppler-derived hyperemic microvascular resistance predicts the occurrence of microvascular injury and microvascular perfusion deficits after successful percutaneous coronary intervention

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Purpose: Between 40 and 50% of patients presenting with ST-segment Elevation Myocardial Infarction (STEMI) develop microvascular injury (MVI) despite complete angiographic restoration of epicardial flow. The purpose of this study was to investigate whether hyperemic microvascular resistance (HMR) immediately following angiographically successful percutaneous coronary intervention (PCI) is related to both occurrence of MVI at cardiovascular magnetic resonance (CMR) and reduced myocardial perfusion at positron emission tomography (PET) as measured in the days following myocardial infarction.
Methods: 60 STEMI patients were included in this prospective study. Immediately after successful PCI, intracoronary pressure-flow derived HMR measurements were performed. CMR cine and late gadolinium enhanced (LGE) imaging and H215O PET imaging were performed 4-6 days after successful PCI. Using CMR, MVI was defined as a subendocardial recess of myocardium with low signal intensity within a gadolinium-enhanced area. Myocardial perfusion was quantified using H215O PET. To define normal values of HMR, 16 patients referred for invasive coronary angiography served as a control group.
Results: Complete datasets were available in 48 patients of which 24 developed MVI. HMR in the culprit artery in patients with MVI was significantly higher than that in patients without MVI (MVI: 3.33±1.50 vs. no MVI: 2.41±1.26, p=0.03). Multivariable analysis showed that HMR was predictive for MVI (p=0.04). High HMR also correlated with decreased myocardial blood flow (MBF) on PET (CFR<2.0: 3.26±1.41 vs. CFR≥2.0: 2.24±1.19; p=0.03).
Conclusion: Elevated Doppler-flow-derived HMR directly following successful primary PCI correlates with CMR-defined MVI and decreased myocardial blood flow measured by PET at follow-up.

P4910 | BEDSIDE
Comparison of conventional and diastolic fractional flow reserve after adenosine and dobutamine infusions for hemodynamic assessment of myocardial bridging

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Introduction: Myocardial bridging (MB) is characterized by dynamic systolic compression of the intramyocardial arterial segment that may impair early diastolic relaxation, as well. It has been suggested that adequate invasive hemodynamic assessment of MB should include inotropic stimulation with dobutamine. Thus, we hypothesized that diastolic fractional flow reserve (FFR) after dobutamine infusion might provide a better insight into the hemodynamic assessment of MB.
Objectives: The aim of the study was to compare conventional and diastolic FFR after adenosine and dobutamine infusions in patients with isolated MB.
Methods: The study included 34 patients (9 males, mean age 56±9 years) with angiographic evidence of MB of the left anterior descending artery (LAD) and systolic compression ≥50% diameter stenosis. Patients were evaluated by SEHO test for detection of myocardial ischemia, and conventional and diastolic FFR in the distal segment of LAD during iv. infusion of adenosine (ADO: 140 μg/kg/min) and iv. infusion of dobutamine (DOB: 10-40 μg/kg/min), separately.
Results: Feasibility for determining FFR during ADO was 32/34 (94%) and during DOB 34/34 (100%), respectively. SEHO test was positive in only 5/34 (15%). Conventional FFR during peak DOB reached similar values as during ADO (0.84+0.07 vs. 0.84+0.05, p=0.35), but diastolic FFR during peak DOB was significantly lower than diastolic FFR during ADO (0.78+0.10 vs. 0.81+0.06, p=0.007). Conventional FFR during ADO and peak DOB was similar between SEHO positive vs. SEHO negative patients (0.83+0.09 vs. 0.84+0.05, p=0.183; 0.80+0.11 vs. 0.84+0.06, p=0.306, respectively). However, diastolic FFR during peak DOB was significantly lower in SEHO positive vs. SEHO negative patients (0.73±0.04 vs. 0.80±0.10, p=0.038), and of borderline significance for ADO (0.78±0.15 vs. 0.82±0.05, p=0.059), respectively. Receiver-operating curve identifies the optimal diastolic FFR DOB cut-off 0.76 (AUC 0.793, 95% CI: 0.650-0.937, p=0.039) with a sensitivity and specificity of 100% and 72%, respectively.
Conclusions: Diastolic, but not conventional FFR measurement during inotropic stimulation, in comparison to vasodilation, provides more reliable functional evaluation of hemodynamic significance of myocardial bridging.

P4911 | BEDSIDE
Effects of electronic cigarette use on arterial elasticity compared to cigarette smoking

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Background: Cigarette smoking has well-established acute and chronic adverse effects on arterial elasticity. This study evaluated the effects of electronic cigarette (EC) use on ascending aorta elasticity and aorta-femoral pulse wave velocity.
Methods: We recruited 84 healthy participants, aged 20-55 years; 42 smokers and 42 daily EC users who had stopped smoking since 11±9 months. Smokers were asked to smoke 2 cigarettes (0.7mg nicotine) and use an EC with nicotine-containing liquid (18mg/ml) for 15 minutes on separate days in a randomized cross-over design. For EC users, examinations were performed at baseline and 20 minutes after using the same EC device and liquid as smokers. Two-dimensional guided M-mode evaluation of systolic (AoS) and diastolic (AoD) diameters of the ascending aorta, 3cm above the aortic valve, was performed at baseline (8 hours abstinence from smoking, alcohol and caffeine), 20 minutes after smoking and 20 minutes after using the EC. Blood pressure and heart rate were also measured. The following aortic elasticity indices were measured: aortic strain = 100 (AoS – AoD)/AoD; aortic distensibility (DIS) = 2(AoS – AoD)/(AoD × pulse pressure); and aortic stiffness index (SI) = ln(SBP/DBP)/[(AoS – AoD)/AoD]. The distance between the aortic arch and the femoral artery was measured (D) and pulse wave velocity (PWV) was assessed by measuring the time from QRS initiation to initiation of blood flow (assessed by pulsed-wave Doppler) at the aortic arch (at the level of the left subclavian artery, AO) and at the level of the right femoral artery (FEM). The formula used was: PWV = D/(flowFEM – flowAO) and was expressed in m/sec.
Results: No difference was observed in baseline characteristics besides higher past daily cigarette consumption in EC users. All measured parameters were similar at baseline. After smoking tobacco cigarettes aortic strain was decreased (from 10.8±4.6 to 8.5±3.4, P<0.001), DIS was decreased (from 3.4±1.6 to 2.8±1.2, P=0.001), stiffness index was increased (from 5.4±2.0 to 7.0±4, P=0.002) and PWV was elevated (from 6.6±1.4 to 6.9±1.6, P=0.004). No difference was observed after EC use in both smokers and EC users.
Conclusion: Arterial elasticity is acutely impaired after smoking tobacco cigarettes, while no immediate adverse effect is observed after EC use.

TESTING AND MAINTAINING PHYSICAL FITNESS: IT'S WORTH THE PAIN

P4912 | BEDSIDE
Physical fitness predicts myocardial infarction and heart failure but only when age-adjusted heart rate response to maximal exercise is low

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Purpose: Physical fitness (PF) has previously been reported to be inversely associated with future CVD risk. We have recently shown that maximal heart rate response to exercise interacts with PF in CVD risk estimation. The present study investigates if PF predicts acute myocardial infarction (MI) and heart failure (HF) independently of heart rate response in 2014 healthy men during 35 yrs follow-up.
Methods: PF, total work divided by body weight (kJ/kg), and heart rate response (bpm), were calculated and age adjusted in 2,014 apparently healthy, middle-aged men after a maximal bicycle exercise test in 1972-75. Events of MI and HF were adjudicated by scrutiny of medical records in all country's hospitals. Risk estimations were analysed in tertiles of PF using univariable and multivariable Cox proportional hazards models.

Results: Crude incidence of MI and HF were 449 (22%) and 99 (5%). Incidences of MI and HF were highest in the lowest PF-tertile (T1). T1 was associated with increased risk of MI and HF compared with T3 both in univariable and multivariable analysis. After stratifying the men by heart rate response, the results for were statistically significant among the men with low heart rate response only (Table).

Table 1

Heart rate response	Event	Low physical fitness (T1) n=677	High physical fitness (T3) n=665
All	MI	1.41 (1.11–1.79)	1
Low	MI	1.96 (1.19–3.47)	1
High	MI	1.14 (0.67–1.88)	1
All	HF	1.70 (1.04–2.82)	1
Low	HF	2.19 (1.03–5.40)	1
High	HF	1.28 (0.56–2.75)	1

Values are hazard ratios (95% CI); MI, myocardial infarction; HF, heart failure. All hazard ratios are adjusted for baseline age, cholesterol, smoking, significant family history of CHD and systolic blood pressure.

Conclusions: Low PF was independently associated with increased risk of MI and HF over 35 yrs in apparently healthy, middle-aged men. After stratification, the prognostic value of PF was confined to the subgroup with poor heart rate response. Thus, assessment of PF and peak heart rate response to exercise may be clinically useful when judging risk of future MI and HF in apparently healthy middle-aged men.

P4913 | BEDSIDE
Cardiopulmonary exercise testing in patients after acute coronary syndrome and PTCA

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Cardiopulmonary exercise testing (CPET) has been recently shown to improve both sensitivity (+89%) and specificity (+15%) of traditional ECG stress test through the analysis of VO2 kinetics that reflects stroke volume and cardiac output during exercise. Between 2009 and 2013 we performed 1113 cardiopulmonary exercise tests (CPET) at the Lancisi Heart Institute's CPET core laboratory in patients (63 (10) years old, 101 women) who underwent PTCA/stenting after acute coronary syndrome (ACS). PTCA/stenting was performed in one (87%) or two coronary vessels (13%). Drug-eluting stents were implanted in 90% of patients. Aim of the study was to discriminate between patients with or without inducible ischemia (i-MI) and to assess prognosis. CPETs were performed on a cycle-ergometer until exhaustion using a ramp protocol. The diagnosis of i-MI by CPET was considered when the following abnormalities were present: 1 mm ST downsloping in two or more adjacent leads; flattening in DVO2/DWR slope (double slope sign); downward flattening in O2pulse.
Results: Of 1113 CPETs, 232 (21%) were positive (CPET+) and 881 (79%) were negative (CPET-). Follow up lasted 28 months on average. Of CPET+ patients, 195 repeated PTCA/stenting for restenosis (75%) or limiting coronary stenosis (15%) or ACS (10%) during the follow-up. Of CPET-, only 5 were hospitalized (ACS in 2, unstable angina in 3). Kaplan Meier analysis showed a significant separation of CPET+ vs CPET- ($P<0.001$ by log rank).
Conclusions: Cardiopulmonary exercise testing may predict the clinical outcome in patients with ACS after PTCA/stenting.

P4914 | BEDSIDE
Physical fitness predicts early but not late myocardial infarction; a 35-year follow-up study of 2,014 healthy middle-aged men

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Background: Physical fitness (PF) has previously been shown to predict cardiovascular (CV) death and disease. In the present study we aimed to investigate how baseline PF influenced risks of myocardial infarction (MI) during the first and last part of a 35 year observation of healthy middle-aged men.
Methods: Age adjusted PF, total work divided by body weight (kJ/kg), was calculated in 2,014 apparently healthy, middle-aged men after a maximal bicycle exercise ECG test in 1972-75. Incident myocardial infarction was registered in a nationwide scrutiny of charts in Norwegian hospitals, and early vs. late event was set before or after median MI-age (66 years). Impact of predictors and relative risks between baseline quartiles of PF were estimated using Cox proportional hazards models. When estimating risks of late MI, men with events before 66 years were excluded.
Results: During follow-up; we found 224 and 225 events of early- respectively late MI. Age adjusted PF at baseline was a significant predictor of early- but not late MI. Family history of CHD, baseline smoking status and cholesterol were significant predictors of early MI, while baseline blood pressure and cholesterol were significant predictors of late MI. Lower PF-quartiles were associated with significantly increased risks of early MI than the highest PF quartile (Q4) in unadjusted, age adjusted and multivariable analysis. There were no differences in risks of late MI among the PF-quartiles (Table).

Hazard ratios (95% CI)

	Early MI	Late MI
PF (1 SD)	0.76 (0.65–0.88)	0.98 (0.83–1.15)
PF Q1	2.18 (1.47–3.30)	1.28 (0.86–1.90)
PF Q2	1.53 (1.01–2.36)	0.99 (0.68–1.46)
PF Q3	1.36 (0.88–2.11)	1.19 (0.83–1.71)
PF Q4	Reference	Reference

PF (1SD), one SD increase of PF; PF Q1–4, quartiles by baseline PF. All hazard ratios are adjusted for baseline age, family history of CHD, cholesterol, smoking and blood pressure.

Conclusions: PF was independently associated with risk of early- but not late MI. Most classical CV risk factors were strong predictors of both early and late MI. Low PF at middle-age could be interpreted as a warning sign of an early rather than late MI.

P4915 | BENCH
Prior moderate and high intensity exercise training similarly attenuate ventricular and autonomic changes induced by myocardial infarction

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Purpose: High intensity interval training (HIIT) has emerged by its additional benefits in patients with cardiovascular disease. However, their cardioprotective role, i.e. when performed prior to myocardial infarction (MI), has been poorly studied. The aim of this study was to compare the efficacy of moderate intensity exercise training (MIET) and HIIT, performed previously to the MI, on ventricular and cardiovascular autonomic responses to ischemic event.
Methods: Male Wistar rats were divided into 4 groups (n=10 each): control (C), sedentary + MI (SI), MIET + MI (MTI) and HIIT + MI (HTI). Trained groups underwent two months of MIET (50-75% of the maximum running speed) and HIIT (with cycles of 90-95% of maximum running speed for 4 min followed by 2 min at 50%), 5 days a week. MI was performed after exercise training (ET) period. After MI, echocardiographic, hemodynamic and autonomic (baroreflex sensitivity, cardiovascular autonomic function) evaluations were conducted.
Results: Independently of intensity, prior ET prevented an additional decline in exercise capacity in MTI and HTI groups in comparison with SI. However, MI area was not modified by previous ET (SI: 45±3; MTI: 42±2; HTI: 43±2%). ET, at both intensities, was able to preserve fractional shortening and E/A wave ratio in MTI (38±1%; 1.8±0.1) and HTI (41±2%; 1.8±0.08) in comparison with SI (30±2%; 2.7±0.2). Similarly, MIET and HIIT prevented the decrease of baroreflex sensitivity in MI animals. Although changes in hemodynamic evaluations were not observed, variance and low frequency band of systolic arterial pressure variability were additionally reduced in HTI (11.7±0.8 and 2.3±0.2 mmHg2) than MTI (25.9±2.7 and 4.3±0.4 mmHg2), as compared with SI (41.0±5.1 and 7.9±0.7 mmHg2). Sympathetic tonus was decreased, while vagal tonus was increased in MTI (-54.7 and +126.0%) and HTI (-52.1 and +178.2%) rats compared with SI.
Conclusions: These results suggest that aerobic ET attenuated cardiac and autonomic dysfunction when performed prior to the MI, independent of training intensity. On the other hand, it is important to highlight that HIIT promotes additional adjustments in the vascular autonomic modulation in relation to MIET. Thus, further studies are necessary in order to investigate the mechanisms associated with these positive adaptations, as well as the possible differences in the training intensity on the prevention of MI abnormalities.

P4916 | BEDSIDE
Increased mortality is related to a low oxygen uptake efficiency slope and inability to reach peak effort in CAD patients

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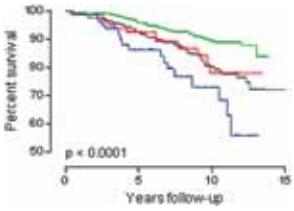
Background: Peak exercise capacity is a well known independent predictor for mortality in patients with coronary artery disease (CAD). However, often exercise tests are stopped prematurely and therefore submaximal measures like the oxygen uptake efficiency slope (OUES) have been introduced. This study sought to determine the prognostic value of the OUES in patients with CAD.
Methods: Patients with CAD, who underwent cardiopulmonary exercise testing (CPET) between 2000 and 2011 were included. OUES was calculated by robust regression analysis. Follow-up information on mortality was collected. Cox regression analyses were used to assess the prognostic value of the OUES and ROC curve analysis was performed. Patient subgroups were established based on the optimal OUES cut-off value and on the ability to reach a peak effort during graded exercise.
Results: In the 1409 CAD patients (mean age 60.7±9.9 years; 1205 men, 204 women), mean OUES was 1538±480. A peak effort could not be reached in 161 (11%) patients. During a follow-up of 7.45±3.20 years (range 0.16 to 14) 158 patients died (68 of cardiovascular causes). OUES was significantly related to all cause (hazard ratio: 0.568, $p<0.001$) and cardiovascular (hazard ratio: 0.461, $p<0.001$) mortality. Survival curves are shown in the figure. Survival was highest

in patients who performed a maximal exercise test and had an OUES >1550 (green; p<0.05) and lowest in patients unable to perform a maximal exercise test and with an OUES ≤1550 (blue). Patients with a maximal test and OUES≤1550 (grey) and patients with a submaximal test and OUES>1550 (red) showed similar survival.



Kaplan-Meier curves.

Conclusion: The OUES is an independent predictor for all cause and cardiovascular mortality in patients with CAD, along with the inability to reach a peak effort during CPET.

P4917 | BEDSIDE
Comparison of two aerobic training interventions in patients with coronary artery disease: the SAINTEX-CAD study

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Background: Exercise-based cardiac rehabilitation is considered an important treatment and secondary preventive measure, but the importance of training modalities such as aerobic interval training (AIT) and moderate continuous training (MCT) in patients with coronary artery disease (CAD) are yet not fully understood.
Aim: To compare, in a multicentre, well powered, randomized study, the effects of AIT and MCT on peak aerobic capacity (peakVO2) and endothelial function (FMD).
Methods: 200 stable CAD patients, with ejection fraction>40%, aged 58±9yrs, 90% male, were randomized to a supervised 12-week cardiac rehabilitation program (CR) of three weekly sessions of either AIT (90% of peak HR) or MCT (75% peak HR). Primary endpoints were data from maximal cardiopulmonary exercise tests (CPET) and FMD before and after CR. Data are presented as mean±SD and comparisons were performed by ANOVA and ANCOVA.
Results: Baseline characteristics and data from the baseline CPET were not significantly different between both groups, except for age (56.5±9 for AIT and 59.2±9 for MCT; p=0.02). 14 and 11 patients dropped out from respectively the AIT and MCT groups, none of them because of exercise related adverse events. Peak VO2 (ml/min/kg) after CR was significantly higher in both groups (F=57.2, p<0.001) and overall higher values were observed in the AIT group (F=4.66, p<0.05). However, no significant time*group interaction was observed and the percent increases of 22.4.9±17.6% for AIT and 20.3±15.3% for MCT were also not significantly different. Inclusion of age as covariant did not alter the results. Endothelial function, as evaluated by FMD, increased also similarly in both groups (19.4% for AIT; 18.2% for MCT; NS).
Conclusion: In contrast to earlier reported studies, this multicentre trial in a larger CAD sample shows equal improvements in aerobic exercise capacity and endothelial function after both aerobic types of exercise training.

P4918 | BEDSIDE
Quality of life post-ACS is related to physical exercise but not to therapeutic interventions

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Introduction: Data from UPBEAT study showed that randomisation of depressed patients with coronary artery disease to a physical exercise program leads to beneficial effects on mood. We performed a real-world registry study to answer the related question of whether engaging in physical exercise post-ACS is associated with quality of life (QoL). A second, unresolved question is to what extent QoL post-ACS is enhanced by medical and therapeutic interventions. These issues are important as QoL determines patients' levels of motivation and compliance.
Methods: The local Swedish SEPHIA registry at our centre which holds data for N=1570 post-ACS patients aged <75 ys was interrogated. QoL was recorded post-ACS at 1 and 12 months as a visual analog scale (EQ-5D) rating, ranging from 0 to 100. Exercise was given in hours/week, non-Scandinavian immigrant status was self-described. Determinants of QoL at 12 months were analysed in backward logistic regression with values above vs. below population median as dichotomous dependent variable. Independent variables were ranked based on Wald statistic.
Results: There were n=1144 cases with complete QoL data (60±9 years; 22% females; 29% non-Scandinavian immigrants). While exercise decreased during follow-up (1 month: 4.9±4.1 vs. 12 months: 4.0±3.0 hs/wk; p<0.001) and smoking increased (14 vs. 18%; p<0.001), QoL did not change (68±21 vs. 70±21; p=NS). The leading independent predictor of high QoL was exercise (OR 1.1 per hr/wk) followed by being working (OR 5.2 vs. being on sick leave), non-smoking (OR 2.3) and being of Scandinavian origin (OR 1.8; p<0.001 for all). Interestingly, while angina (OR 0.52) dyspnoea (OR 0.46) and diabetes (OR 0.52) independently predicted poor QoL, so did medical interventions such as oral treatment with diuretics (OR 0.61), long-acting nitrates (OR 0.58) and ARB (OR 0.55), readmission (any: OR 0.40; for angina: OR 0.35) and PCI (OR 0.63; p<0.05 for all). In fact, not even in univariable testing were there any positive associations between medical or therapeutic interventions and QoL. Importantly, 1-month values of QoL did not independently predict 12-month values, suggesting associations seen are not explained by reverse causality.
Conclusion: In post-ACS patients, physical exercise is strongly associated with high QoL. Whether the "feelgood effect" of exercise translates into better patient compliance and clinical benefit remains to be shown. Disappointly, while comorbid patients suffer from poor QoL, the impact of commonly recommended medical interventions appears to be neutral or even detrimental.

PHARMACOTHERAPEUTIC CHALLENGES IN THE REAL WORLD

P4919 | SPOTLIGHT
Evaluation of effectiveness and cost effectiveness of decision support system in managing hypertension in resource constrained primary health care settings: results from a cluster randomised trial

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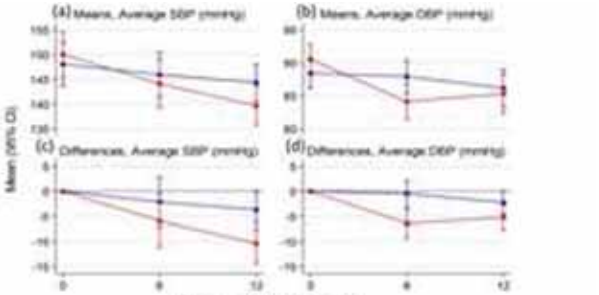
Background: With increasing adoption of information technology in healthcare domains and a shortage of healthcare workforce conversant with guideline-based clinical management, there is need to assess the utility of a clinical decision support system for providing evidence based healthcare and in reducing patient outcomes in resource constrained Primary Health Centre (PHC) settings
Trial design: Cluster randomised trial
Participants: Hypertensive patients between 35-64 years of age reporting to PHCs of Mahabubnagar district, Andhra Pradesh, India.
Interventions: (1) Clinical Decision Support System (DSS) (2) Chart Based Support (CBS)
Objective: To test the effectiveness and cost effectiveness of a clinical DSS among hypertensive patients in India.



Comparison of BP between DSS and CBS arm.

Abstract P4917 – Table 1

Variable	AIT pre	AIT post	MCT Pre	MCT Post	F Time	F Group	F interaction
Peak VO2 (ml/min/kg)	23.3±5.8	28.4±6.9	22.2±5.6	26.8±6.7	57.2; p<0.001	4.66; p<0.05	0.16 (NS)
Peak RER	1.26±0.11	1.28±0.11	1.27±0.11	1.27±0.09	1.13 (NS)	0.21 (NS)	0.65 (NS)
Peak HR (b/min)	135±21	145±19	129±21	138±22	20.9; p<0.001	7.58; p<0.01	0.04 (NS)
HR rest (b/min)	68.4±11.7	66.8±10.2	67.7±12.3	64.7±10.4	3.78; p=0.052	1.38 (NS)	0.33 (NS)
FMD (%)	5.51±3.18	6.58±2.88	5.71±2.50	6.75±3.06	11.5; p<0.001	0.35 (NS)	0.00 (NS)

Primary outcome: Mean changes in systolic blood pressure (SBP) from baseline to 12 months among hypertensive patients randomized by PHC to receive the DSS or the chart based algorithmic support system.
Randomisation: Computer generated cluster-randomization.
Blinding/masking: Blinded to participants and statistician.
Results: The mean difference at 12 months between the CBS and DSS groups adjusted for age, gender, height, waist, body mass index, alcohol intake, pickle and papad (salty food) intake, and portions of vegetable/fruit consumed per day, systolic BP was -6.59 mm of Hg (95% CI: -12.18 to -1.42, p=0.021) and for diastolic BP was -2.83 mm of Hg (95% CI: -5.78 to 0.13, p=0.083). The incremental cost effectiveness ratio for DSS when compared with CBS was $335.37 per QALY gained (95%CI: $252.34 – $416.27).
Conclusion: Clinical DSS are effective in the management of hypertension and are cost effective in primary care settings
Trial registration: CTRI/2012/03/002476; Clinical Trial Registry of India

P4920 | BEDSIDE
Long-term effects of L- and N-type channel blocker on serum uric acid levels and left atrial volume in hypertensive patients

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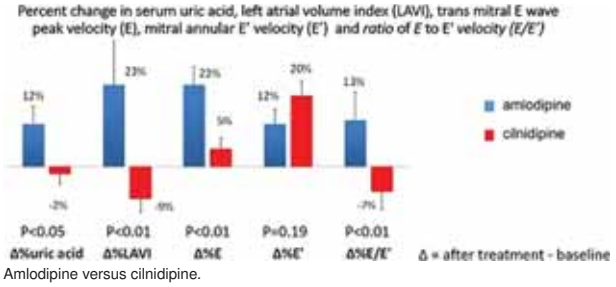
This study was designed to investigate whether the L- and N-type channel blocker, Cilnidipine, may affect LV diastolic function differently compared with the L-type channel blocker, Amlodipine in patients with essential hypertension.
We studied 49 patients with untreated hypertension, randomly assigned to Cilnidipine (Cil) or Amlodipine (Aml) for 48 weeks. LV diastolic function was assessed with the Left atrial volume index (LAVI), mitral early diastolic (E) wave, tissue Doppler early diastolic velocity (E') and the ratio (E/E'). Plasma aldosterone (PAC) and uric acid were measured as markers of myocardial fibrosis and inflammation before and after treatment.
Results: Systolic and diastolic blood pressures equally dropped in both groups. LAVI and E/E' decreased in the Cil group but not in the Aml group. There was no significant change in heart rate or PAC in both groups. Serum uric acid significantly increased in the Aml group but not in the Cil group. LAVI, E/E' and serum uric acid levels significantly decreased after 48 weeks of treatment with Cil group but not with Aml group (-9±4 vs. 23±14%, $p<0.05$, -7±5 vs. 13±8%, $p<0.05$, -2±3 vs. 12±5%, $p<0.05$ as percentage reduction from the values before treatment). Larger %-drop in serum uric acid and E/E' were associated with larger %-reduction of LAVI (r=0.50, $p<0.01$, r=0.40, $p<0.01$). Multiple regression analysis showed that the changes in the LAVI is related to the changes in the serum uric acid (r=0.47, $p<0.01$)



Amlodipine versus cilnidipine.

Conclusions: Cilnidipine but not Amlodipine may improve LV diastolic function in hypertensive patients, at least partially through the attenuation of myocardial fibrosis by regulating oxidative stress.

P4921 | BEDSIDE
Chronopharmacotherapy of hypertension is crucial in mortality in patients with coronary heart disease

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Purpose: The goal of our study was to assess the influence of hypertension chronopharmacotherapy on diurnal blood pressure (BP) profile and mortality.
Methods: Subjects with established coronary heart disease (CHD) (n=1345, mean age 63.2±9.2 years) were included. Clinic BP measurement was performed and 24-hour ambulatory BP monitoring was obtained. The percentage decrease in mean BP during the nighttime period was calculated as 100x[daytime BP mean – nighttime BP mean]/daytime BP mean. Using this percentage ratio, subjects were classified as dippers or non-dippers (nighttime relative BP decline ≥or <10%, respectively). The present study is a part of PROGNOSIS study.
Results: The median follow-up period was 6.6 years. Antihypertensive treatment is presented in table. Non-dipping status was related to a lack of nighttime hypertensive drug administration (OR 3.87, 95%CI 3.00-4.98). In a Cox proportional hazards regression model, non-dipping status (HR 1.17, 95%CI 1.02-1.47) and non-nighttime antihypertensive drug administration (HR 1.13, 95% CI 1.01-1.45) were predictors of all-cause mortality.

Antihypertensive treatment

	Dippers n=600	Non dippers n=745	P
Nitrate, n	174 (29%)	246 (33%)	ns
β-blockers, n	444 (74%)	589 (79%)	ns
Calcium channel blockers, n	150 (25%)	186 (25%)	ns
ACE-I/ARBs n	438 (73%)	544 (73%)	ns
Diuretics, n	78 (13%)	89 (12%)	ns
α-blockers, n	18 (3%)	37 (5%)	ns
One medication, n	150 (25%)	194 (26%)	ns
Two medications, n	312 (52%)	365 (49%)	ns
Three or more medications, n	138 (23%)	186 (25%)	ns
Only morning administration of drugs, n	180 (30%)	484 (65%)	<0.01
Only evening administration of drugs, n	78 (13%)	60 (8%)	ns
Twice a day administration of drugs, n	168 (28%)	104 (14%)	<0.03
Three or more times a day administration of drugs, n	174 (29%)	97 (13%)	<0.01

ACE-I, inhibitors of angiotensin converting enzyme, ARBs-angiotensin receptor blockers.

Conclusions: The non-dipping profile of CHD patients and increased mortality were related to a lack of antihypertensive drug administration at bedtime.

P4922 | BENCH
Biological properties of adrenomedullin conjugated with polyethylene glycol

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Purpose: Adrenomedullin (AM) is a vasodilator peptide having pleiotropic effects including cardiovascular protection and angiogenesis. Because of these beneficial effects, AM appears to be a promising therapeutic tool for human diseases such as myocardial infarction or peripheral artery disease, while intravenous injection of AM stimulates sympathetic nerve activity due to the short-acting potent vasodilation, resulting in increased heart rate and renin secretion. To lessen those acute unfavorable actions, we conjugated the N-terminal of human AM with polyethylene glycol (PEG), and examined biological properties of PEGylated AM in the present study.
Methods: N-terminal of synthesized human AM peptide was conjugated with PEG5000-NHS, and then PEGylated AM was obtained by purification with HPLC. Biological effects in vitro stimulating intracellular cAMP, a major second messenger of AM, were examined using cultured human embryonic kidney (HEK)-293 cells stably expressing a specific AM receptor. Blood pressure-lowering effects in vivo were tested by intravenous injections of PEGylated or native AM peptides into anesthetized rats. Plasma disappearance curves of peptides were evaluated by the two compartment model.
Results: PEGylated AM stimulated intracellular accumulation of cAMP in cultured HEK-293 cells, as did native human AM peptide, in a dose-dependent manner. pEC50 of PEGylated AM was lower than native AM (8.19±0.10 vs. 8.59±0.90, mean ± SEM, $P<0.05$), but no difference was noted in the maximum response of cAMP (9.44±0.30 vs. 9.30±0.26 nmol/well). When injected intravenously at the dose of 10 nmol/kg, both peptides lowered blood pressure (BP) in anesthetized rats, while the acute reductions in mean BP of PEGylated AM were substantially smaller than those of native AM at 2 min (-11.5±1.5 vs. -24.5±3.2 mmHg, $P<0.01$) and at 4 min (-9.7±1.5 vs. -20.0±2.9 mmHg, $P<0.05$) of the injection. The first and second plasma half-lives of PEGylated AM were 4.87±0.68 and 108±12 min, while those of native AM were 0.62±0.02 and 15.2±1.9 min, respectively. Both half-lives of the PEGylated peptide were significantly prolonged, as compared with the native peptide ($P<0.05$).
Conclusions: N-terminally PEGylated AM stimulated cAMP production in vitro, showing smaller acute hypotensive action and a prolonged plasma half-life in comparison of native AM peptide in vivo. The present results suggest a possibility for PEGylated AM as a therapeutic tool with lessened unfavorable effect of acute hypotension of native AM.

P4923 | BENCH
Combination therapy with lercanidipine and enalapril improves wave reflection in hypertensive patients with metabolic syndrome

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Arterial stiffness and wave reflection are independent predictors of cardiovascular events. In a randomized, open, parallel group study we compared the effect on these parameters of a combination therapy with an ACE-inhibitor plus calcium channel blocker or thiazide diuretic in 76 hypertensive patients with metabolic syndrome uncontrolled by ACE-inhibitor monotherapy.
After 4 weeks run-in with enalapril (ENA, 20 mg), patients were randomized to a combination therapy with lercanidipine (LER, 10-20 mg) or hydrochlorothiazide (HCT, 12.5-25 mg) for 24 weeks. Aortic stiffness (carotid to femoral pulse wave

velocity, PWV), central blood pressure (BP) and wave reflection (augmentation index, AIx) were measured by applanation tonometry.
After run-in office BP was similar in the two groups. (ENA/LER: 149±5/95±2; ENA/HCT 150±5/95 mmHg). Office (ENA/LER 132±10/82±5; ENA/HCT 133±7/83±5 mmHg), 24-hour (ENA/LER 123±11/75±7; ENA/HCT 122±12/77±7 mmHg) and central BP (ENA/LER 121±13/80±9; ENA/HCT 122±13/79±9 mmHg) were similarly reduced after 24 weeks. PWV was similar after run-in and equally reduced by the two treatments (ENA/LER from 8.6±1.5 to 8.1±1.3 m/s, $p<0.05$; ENA/HCT from 8.5±1.2 to 8.2±1.0 m/s, $p<0.05$). Finally, both combinations reduced AIx, but its reduction resulted significantly greater ($p<0.05$) in ENA/LER (from 26.8±10.9 to 20.6±9.1%) than in ENA/HCT arm (from 28.2±9.0 to 24.7±8.7%).
In conclusion, the combination with LER caused a similar PWV reduction as compared to HCT, but a greater reduction in AIx in hypertensive patients with metabolic syndrome not controlled by ENA alone. These results indicate a positive effect of the combination of ENA/LER on wave reflection, suggesting a potential additive role for cardiovascular protection.

P4924 | BEDSIDE
Prevalence and evaluation of erectile dysfunction in the practice of the specialized cardiology clinic in Northern Malaysia

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Vascologenic or drug-induced erectile dysfunction (ED) is prevalent among cardiac patients in whom it affects their quality of life and medication taking behavior. European cardiology practice guidelines recommend assessment of ED during regular follow-up in order to further predict any medication non-adherence or serious interactions that might occur when mixing between nitrates or antiarrhythmias with the phosphodiesterase-5 inhibitors (PDE5-Is). In Malaysia, the latest published cardiac diseases-treatment guidelines did not contain information about sexual counselling or ED evaluation. This study aimed to explore the prevalence of ED in addition to knowing patients' previous experience and future perspective to discuss and manage sexual dysfunction by health care team in the specialized cardiology clinic in Northern Malaysia.
The Malay version of the abridged International Index of the Erectile Function (5-IIEF) was used to determine the presence and severity of ED among a convenient sample of 329 selected cardiac patients who were eligible to respond to the questionnaire. The majority of respondents (88.1%; 289 patients) had symptoms of ED with a mean score of 15.9 (±5.2) indicating an overall moderate severity. The total score was significantly correlated with age (-0.319; $P<0.01$) in line with the evidence that ED is worsened by age. Among all other measured variables, only diuretics (7.07; $P<0.01$) and diagnosis of dysrhythmia (4.35; $P<0.05$) were significantly associated with ED. Only 38 patients (11.6%) reported a history of trying ED medications where all the uses were without a medical prescription. In respect to the experience of sexual counseling, 87.8% of the sample reported "never received any sexual counseling or asked about ED while been followed-up". On the other hand, 73.7% reported being comfortable to discuss sexual issues with the cardiologists in the future. The rest 24.9% were uncomfortable as their main reason was shyness due to lack of privacy in the crowded clinic.
This finding reveals a high prevalence of ED among cardiac patients with low tendency of treatment by cardiologists. A limited and unmonitored use of PDE5-Is could be due to economic factors that refrain patients from seeking appropriate ED treatment by specialists outside the cardiology clinic. Since majority of the patients are okay with discussing issues of sexual dysfunction in the clinic, we recommend issuing a statement to be added to the clinical guidelines for a structured treatment and sexual counseling in general as well as ED assessment for males in the cardiology practice.

REMODELLING AND DEATH OF CARDIAC MYOCYTES

P4925 | BENCH
Inhibition of the ubiquitin ligase atrogin-1 impairs chmp2b turnover, blocks autophagy flux and causes cardiomyopathy

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Purpose: Control of cardiomyocyte (CM) proteostasis operated by the ubiquitin/proteasome (UPS) and autophagy/lysosome systems is fundamental for heart adaptation to both physiologic and pathologic stresses. Reduced efficiency of either UPS or autophagy/lysosome system occur during ageing and has been associated to cardiomyopathies. Atrogin-1 is a muscle specific ubiquitin ligase, targeting for degradation signalling proteins involved in cardiac hypertrophy. However, the role of Atrogin-1 in CM biology and its involvement in the molecular mechanism of cardiac dysfunction, are largely unexplored.
Methods: We analyzed hearts from Atrogin-1 knock-out (KO) mice from 6 mo. onwards until death, and compared it to that of age- and sex-matched controls. Functional, immunofluorescence and electron microscopy analyses were performed. Markers of ER/SR stress and autophagy/lysosome systems were investigated by RTqPCR and WB. In vivo pulsed SILAC proteomics and bioinformatics, Co-IP, in vitro assays and in vivo viral silencing were performed to identify novel targets of Atrogin-1.
Results: By using in vivo and in vitro assays we identified a novel target of Atrogin-1, the ESCRTIII protein CHMP2B, that plays a fundamental role in autophagy. Failure to degrade CHMP2B in Atrogin-1 KO mice caused autophagy impairment, accumulation of intracellular protein aggregates, activation of the unfolded protein response and subsequent CM apoptosis, all of which increased progressively during ageing. The alterations in cellular proteostasis resulted in cardiomyopathy with a restrictive pattern, characterized by myocardial remodelling with interstitial fibrosis, diastolic dysfunction (Edt, KO: 20.7±2.7 vs WT: 27.8±5.7, in msec), arrhythmias and secondary LA and ventricular remodelling, as well as CM hypertrophy (CM area, KO: 289.34±2.23 vs WT: 236.77±1.64, in μm^2). Aged Atrogin-1 KO mice had reduced tolerance to treadmill exercise compared to controls, and shortened life span (KO: 17±1 vs WT: 24±1.2, in mo.). In vivo reduction of CHMP2B protein level in the KO mice restored normal autophagy and protected CMs from cell death resulting from CHMP2B proteotoxicity.
Conclusions: Our data highlight the importance of regulated proteolysis in the heart and show that the loss of Atrogin-1 per se is sufficient to cause cardiac damage, which evolves into cardiomyopathy when protein quality control becomes less efficient, as occurring in aging. Such cardiomyopathy represents a novel model of proteotoxic myocardial remodelling and will be useful to determine the mechanism of impaired proteostasis to CM damage.

P4926 | BENCH
Omentin plays a crucial role in the regulation of cardiac hypertrophy

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Background: Cardiac hypertrophy occurs in many obesity-related conditions. Omentin is an adipose-derived plasma protein that is downregulated under obese conditions. Recently, we have reported that plasma omentin levels are decreased in obesity-linked disorders including ischemic heart disease. Here, we investigated whether omentin modulates cardiac hypertrophic responses in vivo and in vitro.
Methods: The in vivo pathological cardiac hypertrophy models were induced by transverse aortic constriction (TAC) and angiotensin (Ang) II infusion (3.2mg/kg/day) in wild-type (WT) mice, and the in vitro hypertrophic response was induced by phenylephrine (PE) or endothelin-1 (ET-1) exposure to cultured cardiomyocytes.
Results: Treatment with adenoviral vector expressing human omentin (Ad-OMT) attenuated the increase in heart weight (HW)/ body weight (BW) ratio after the TAC or Ang II infusion. Echocardiographic analysis of cardiac structure also revealed that administration of Ad-OMT reduced the TAC or Ang II-induced increase in left ventricular wall thickness. Treatment with Ad-OMT attenuated myocytes cross-sectional area and fibrosis, and extracellular signal-regulated kinase (ERK) phosphorylation after the TAC surgery or Ang II infusion. Furthermore, we generated transgenic mice featuring the human omentin gene under the control of the aP2 promoter. Cardiac hypertrophy induced by TAC or Ang II infusion was attenuated in transgenic mice overexpressing human omentin compared to littermate control mice. Treatment of cardiomyocytes with PE or ET-1 induced an increase in myocyte size, which was associated with reorganization of sarcomeric actin, and this induction was suppressed by pretreatment with recombinant omentin protein. Pretreatment with omentin also reduced ERK phosphorylation in response to PE or ET-1 stimulation. Inhibition of AMPK activity by transduction with dominant-negative mutant forms of AMPK (dn-AMPK) reversed the inhibitory effect of omentin on myocyte hypertrophy and ERK phosphorylation in PE-treated cardiac myocytes. Moreover, the protective effects of omentin on TAC-induced cardiac dysfunction were abolished in muscle-specific transgenic mice expressing dn-AMPK.
Conclusion: Our findings suggest that omentin functions to attenuate the pathological process of myocardial hypertrophy via an AMPK-dependent mechanism, suggesting that omentin may represent a therapeutic target molecule for treatment of cardiac hypertrophy.

P4927 | BENCH
The soluble guanylate cyclase activator cinaciguat prevents pressure overload-induced cardiac hypertrophy

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Purpose: Pathological cardiac hypertrophy is observed in pressure overload of the left ventricle. Elevated intracellular cGMP-levels have been reported to prevent the development of pathological myocardial hypertrophy. We investigated the effects of chronic activation of the cGMP producing enzyme, soluble guanylate cyclase (sGC) by cinaciguat in a rat model of pressure overload-induced cardiac hypertrophy.
Methods: We performed aortic banding (AB) to evoke pressure overload-induced cardiac hypertrophy in our rats. Sham operated animals served as controls. Experimental groups were treated with 10 mg/kg/day cinaciguat (Cin) or with placebo (Co) p.o., respectively. Development of cardiac hypertrophy was investigated by echocardiography. We performed left ventricular (LV) pressure-volume analysis with a pressure-conductance microcatheter to assess cardiac function. In addition to our functional experiments, histological and molecular biological measurements were carried out.
Results: Echocardiography showed marked myocardial hypertrophy in the AB-Co group (left ventricular mass index (LVMi): 3.15±0.09 AB-Co vs. 2.13±0.04 g/ttkg Sham-Co) which was verified by post mortem investigation of the hearts (heart weight/tibial length ratio (HW/TL): 0.384±0.015 AB-Co vs. 0.293±0.008 g/cm Sham-Co) and by histology (cardiomyocyte diameter (CD): 17.37±0.04 AB-Co vs. 14.55±0.12 μm Sham-Co). Increased left ventricular dimensions (left ventricular end-diastolic volume: 414±19 AB-Co vs. 341±19 μl Sham-Co) were observed while ejection fraction and fractional shortening remained unchanged. Cinaciguat did not alter blood pressure but effectively attenuated left ventricular hypertrophy (LVMi: 2.64±0.06 g/ttkg, HW/TL: 0.339±0.009 g/cm, CD: 15.08±0.10μm, $p<0,05$ vs. AB-Co).
Conclusions: Our results demonstrate that chronic stimulation of the NO-cGMP signalling by pharmacologically activating soluble guanylate cyclase might be a novel therapeutic approach in the prevention of pathological myocardial hypertrophy.
Supported by the grant OTKA10555.

P4928 | BENCH
Small heterodimer partner blocks cardiac hypertrophy by interfering with GATA6 signaling

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Rationale: Small heterodimer partner (SHP; NR0B2) is an atypical orphan nuclear receptor that lacks a conventional DNA binding domain. By interacting with other transcription factors, SHP regulates diverse biological events including glucose metabolism in liver. The role of SHP in adult heart diseases has not yet been demonstrated.
Objective: We aimed to investigate the role of SHP in adult heart in association with cardiac hypertrophy.
Methods and results: The roles of SHP in cardiac hypertrophy were tested in primary cultured cardiomyocytes and in animal models. SHP null mice showed a hypertrophic phenotype. Hypertrophic stresses repressed the expression of SHP, whereas forced expression of SHP blocked the development of cardiomyocyte hypertrophy. SHP reduced the protein amount of Gata6. By direct physical interaction with Gata6, SHP interfered with the binding of Gata6 to GATA binding elements in the promoter regions of natriuretic peptide precursor type A. Metformin, an anti-diabetic agent, induced SHP and suppressed cardiac hypertrophy. The metformin-induced anti-hypertrophic effect was attenuated either by SHP siRNA in cardiomyocytes or in SHP null mice.
Conclusions: These results establish SHP as a novel anti-hypertrophic regulator that acts by interfering with GATA6 signaling. SHP may participate in the metformin-induced anti-hypertrophic response.

P4929 | BENCH
Deletion of wnt signaling in macrophages improves cardiac remodeling and function after MI in mouse

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Background: Macrophages control the initiation, maintenance and resolution of the inflammatory response after acute myocardial infarction (MI). Recently, macrophage-derived Wnt signaling has emerged as a key mediator in development, inflammation and repair. However, its role in MI remains undetermined. Therefore, the aim of our study was to investigate the role of Wnt pathway signaling in cardiac repair and regeneration, and to assess its specific role in macrophages by using a cre-lox conditional transgenic strategy.
Methods and results: To assess Wnt signaling after MI, mice were subjected to anterior MI by left coronary artery occlusion or sham operation (controls). Hearts were harvested for RNA purification and Wnt signaling analysis was performed using real-time PCR array for Wnt pathway components. Notably, genes associated with active Wnt signaling, such as Wisp1, Lef1 and Fzd3 were up-regulated in the infarcted myocardium, compared with controls. A histological assessment of beta-catenin, an important downstream component of the canonical Wnt signaling pathway, showed this signaling to be highly expressed in the infarct area only, at the site of macrophage accumulation. Next, we induced anterior MI in transgenic mice that could not produce Wnt ligands from macrophages (Cfms-icre;Wlsfl/fl). We then evaluated cardiac function by echocardiography measurements, 1, 7 and 30 days after MI. Interestingly, we found that Wnt signaling ablation in macrophages had a protective effect against adverse cardiac remodeling and dysfunction. Specifically, left ventricular (LV) dilatation was lower and ejection fraction higher in mice with macrophage Wnt signaling deletion, compared with wild-types.
Conclusion: A Wnt signaling pathway is up-regulated in the infarcted heart. Our findings suggest, for the first time, that inhibition of this pathway in macrophages attenuates adverse LV remodeling and improves heart function. Thus, the macrophage-derived Wnt family of proteins could be a potential therapeutic target for cardiac repair and regeneration.

P4930 | BENCH
Nuclear calcineurin is a sensor for detecting Ca2+ release from the nuclear envelope via IP3R

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Background: We hypothesize that decoding Ca2+ signals for hypertrophic signaling in continuously beating cells like cardiac myocytes with rapid alterations of cytosolic Ca2+ levels requires intracellular Ca2+ microdomains that are partly independent from cytosolic Ca2+. Further there is a need for a Ca2+ sensor within this microdomain that translates Ca2+ signals into hypertrophic signaling. Recent evidence suggested that the nucleus of cardiac myocytes might be a Ca2+ microdomain and that calcineurin, once translocated into the nucleus could act as a nuclear Ca2+ sensor.
Methods and results: Employing a transgenic mouse model with conditional calpain inhibition we now demonstrate that calpain-truncated calcineurin escaped further degradation by the UPS in the nucleus and could not be relocated to the cytosol. Truncated nuclear calcineurin was able to act as nuclear Ca2+ sensor detecting local Ca2+ release from the nuclear envelope via IP3R. Nuclear calcineurin mutants defective for Ca2+ activation failed to activate NFAT dependent transcription. Under hypertrophic conditions Ca2+ transients in the nuclear microdomain were significantly higher than in the cytosol providing a basis for sustained calcineurin/NFAT mediated signaling uncoupled from cytosolic Ca2+.
Conclusion: These data provide an explanation how Ca2+ and calcineurin might regulate transcription in cardiomyocytes in response to neurohumoral signals independently from their role in cardiac contraction control.

P4931 | BENCH
Toll-like receptor 2 deficiency preserves cardiac diastolic function in pressure overload induced heart failure

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Introduction: Approximately 50% of the heart failure patients have a preserved ejection fraction (HFPEF). While as deadly as heart failure with reduced ejection fraction (HFREF) the mechanisms underlying HFPEF remain unclear. Toll-like receptor 2 (TLR2) is part of the innate immune system and detects exogenous bacterial ligands but also endogenous ligands. TLR2 has shown to be involved in the inflammatory response following ischemia reperfusion injury and HFREF. Although inflammation is also important in HFPEF, a role for TLR2 in HFPEF has not been explored.
Methods: C57BL/6J and TLR2 deficient mice were subjected to transverse aortic constriction (TAC) via intercostal incision. The presence of TAC was confirmed by echocardiography. Cardiac function was analyzed with echocardiography at baseline, 3 weeks and 8 weeks after TAC. Animals with an Ejection Fraction (EF)<40% at 3 and 8 weeks (25%) were excluded.
Results: Eight weeks after TAC, 7 wild type (WT) and 11 TLR2 deficient (TLR2KO) had an EF >40%. The end systolic (ESV) and diastolic volumes (EDV) of left ventricle (LV) increased in WT mice but not in TLR2KO mice (ESV: 36.05±2.02μL for WT vs 27.09±2.28μL for TLR2KO, p=0.0118; EDV: 74.14±3.80μL for WT vs 57.96±4.12μL for TLR2KO, p=0.0031). After TAC, the LV weight determined by echocardiography increased similarly for WT and TLR2KO mice. The mitral inflow E/A ratio as the parameter for ventricular stiffness, however, significantly decreased in WT mice but not in TLR2KO mice re-

sulting in a significant lower (p<0.01) E/A ratio in WT compared to TLR2KO at 8 weeks after TAC. Preservation of E/A ratio indicates that TLR2 deficiency attenuated the pressure overload-induced increase of LV stiffness.
Conclusion: TLR2 is involved in HFPEF induced by TAC. TLR2 deficiency leads to a reduced ventricular stiffness identifying TLR2 as a potential target for treatment of HFPEF.

IMAGING RIGHT

P4932 | BEDSIDE
Predictive ability of right ventricular free wall strain in chronic versus acute pressure overload

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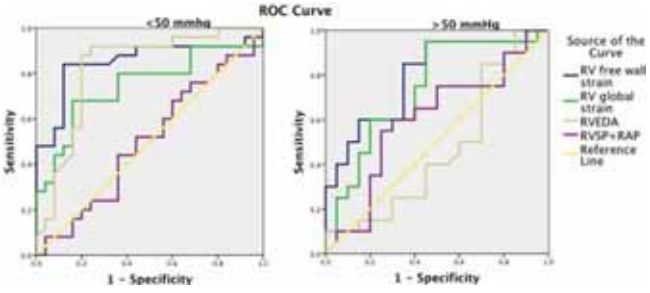
Purpose: Acute pulmonary embolism (PE) is an important cause of morbidity and mortality. Efforts to differentiate right ventricular (RV) failure from chronic (eg. pulmonary hypertension [PHT]) vs. acute pressure overload have had limited success. We proposed that assessment of RV deformation using RV free wall strain (RVS) would discriminate acute PE from chronic PHT.
Methods: 45 PE pts (64±15 yrs, 15 men) were matched for age, gender and RV systolic pressure (TR mmHg + Right atrial pressure) with 45 PHT pts. Standard echo measurements were performed following ASE guidelines. RVS was performed using VVI. Receiver operating characteristic (ROC) curve analyses and incremental multivariate analysis were performed to analyze significant associations of etiology of RV pressure overload. Anticipated associations were placed into the models (age, sex, RV end-diastolic area [EDA] and fractional area change [FAC]).
Results: RVSP was similar in PE (48±18 mmHg) and PHT (46±17, p=.61). PE pts displayed significantly lower FAC (26±12 vs. 38±12%, p<0.001) & RVS (-13.6±5.7 vs. -19.6±4.7% p<0.001), but increased RVEDA (25±6 vs. 21±7 cm^2, p=0.007). ROC analyses revealed that RV strain had excellent discriminative power (AUC 0.82). Recognition of PE in pts with RVSP <50 mmHg with RVS (AUC 0.85) showed 84% sensitivity and 88% specificity with a cutoff of -17.4%. With RVSP >50 mmHg, RVS of -16.3% (AUC 0.79) showed 85% sensitivity and 65% specificity (Figure). In a stepwise model, addition of RVS increased the model chi square from 25 to 31 (p=0.003)



Conclusion: At the same level of PA pressure, RVS is sensitive for detecting acute PE. This relationship changes at different pressure loads within the RV. Strain is superior to traditional markers of RV assessment such as RVEDA and FAC.

P4933 | BEDSIDE
Right ventricular systolic function and exercise capacity in chronic systolic heart failure: right ventricular mechanics outperform conventional echocardiographic parameters

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Background: In patients with chronic systolic heart failure (CHF), decreased peak exercise capacity predicts cardiovascular outcomes and determines advanced heart failure therapies consideration. Right ventricular (RV) function has been previously recognized as a major determinant of exercise capacity in CHF patients. RV function assessment by longitudinal peak systolic strain (LPSS) has proven to have superior correlation with right heart catheterization indices of RV function than conventional echocardiographic measurements like tricuspid annular plane systolic excursion (TAPSE). We sought to compare multiple echocardiographic parameters of RV function with LPSS as predictors of peak exercise capacity in stable CHF patients, which has not been previously reported.
Methods: Fifty consecutive ambulatory patients with chronic systolic HF (left ventricular ejection fraction [LVEF] ≤45%) underwent symptom-limited cardiopulmonary exercise testing and transthoracic echocardiography including LPSS, TAPSE, tricuspid annular peak systolic velocity (s'), RV fractional area change (FAC), and RV myocardial performance index (Tei index).
Results: In our study cohort (mean age 52±13 years, 78% male and mean LV ejection fraction 30±7%), the mean RV LPSS was -21±7%, RV s' 10±2 cm/s, RV FAC 0.43±0.1, Tei index 0.6±0.2 and median TAPSE 18 mm (IQR: 16 to 21). Peak oxygen uptake (pVO2) was 18.9±5.7 ml/kg/min, exercise duration 11.0 minutes (IQR: 9.1 to 12.6), and VE/VCO2 33.3±5.7. In the univariate analysis, RV LPSS (r=0.46, p=0.003) and RV FAC (r=0.34, p=0.02) had a direct correlation with pVO2, while Tei index showed an inverse correlation (r= -0.32, p=0.02). Additionally, RV LPSS was directly correlated with exercise time (r=0.39, p=0.01) and inversely correlated with VE/VCO2 (r= -0.37, p=0.02). In the multivariate analysis, only RV LPSS and FAC were independently associated to pVO2 after adjusting for age, male gender and LVEF.
Conclusions: In stable CHF patients, RV function by LPSS is an independent predictor of decreased pVO2 and has the best correlation with exercise capacity when compared with conventional echocardiographic parameters.

P4934 | BEDSIDE
Two and three-dimensional echocardiographic assessment of right atrial size and function in relation to clinical, hemodynamic characteristics and mortality in patients with pulmonary hypertension

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Right atrial (RA) size and function can be a good predictor of clinical outcome in patients (pts) with pulmonary hypertension (PH). We aimed to assess the RA volumes (V) and functions by two-dimensional and three-dimesional echocardiography (2DE, 3DE), and to evaluate the relationship among 2DE and 3DE measures and functional class (FC), six-minute walking distance (6MWD), plasma brain natriuretic peptide (BNP) level and hemodynamic measures (HM) in pts with PH.
Fifty one pts with PH (age 43±14 years, F 31,M 20) and 20 healthy age and sex-matched controls were included into the study. Subgroups of PH were as follows:Idiopathic pulmonary arterial hypertension (IPAH) in 18 pts,PAH associated with congenital heart defects (APAH-CHD)in 26 pts, Scleroderma-APAH in 1pt, Group 3 PH in 2 pts,Group 4 PH in 2 pts, and Group 5 in 2pts. 2D and 3D TTE examinations were performed by Phillips EI33 system and X5-1 probe. RV sistolic function was assessed by tricuspid annular planary systolic excursion and tissue velocity (TAPSE and St). Maximum, pre-atrial contraction and minimum RA volumes (Vmax, VpreA and Vmin), total, passive and active emptying fractions (TotEF%;PasEF%; ActEF%) and RA global longitudinal strain (GLS) were measured. PH pts had greater 3DE and 2DE RA volumes compared with controls (p<0,0001). Etiological PH subgroups had comparable TAPSE, St, RA volumes and GLS (p=NS). 3DE RA Vmax and Vmin were significantly higher compared to 2DE volumes (p<0,0001 and p<0,05) whereas EF % were similar (p=NS). 3DE RA Vmax,Vmin and TotEF% correlated with Uric Acid (UA) (R=0,31, 0,34 and -0,31, p<0,05), TAPSE (R= -0,46, -0,50 and 0,49, p=0,0001, <0,0001 and <0,0001), St (R= -0,41, -0,470 and 0,50, p=0,003, 0,0001 and <0,01) and inferior vena cava diameter (IVCd) (R=0,64,0,64 and -0,42, p<0,0001, 0,0001 and <0,001),respectively. Ageing was associated with a decrease in 3DTotEF (r= -0,372 p: 0,007). TAPSE, St and IVCd showed good correlations with 2DRAVmax, Vmin, VpreA; 2DTotEF% (r=0,62; 0,50 and -0,58) and GLS (r=0,57; 0,65 and -0,41) (all p<0,001). 6MWD correlated with TAPSE and 2D TotEF% (r=0,35 and 0,32, p<0,05) and BNP correlated with 2D Vmax and Vmin and 3D Vmin (0,33,0,39 and 0,32, p<0,05),respectively. Moreover, 6MWD (p=0,0001), UA (p=0,004),3D and 2D RA Vmax (p=0,003 and 0,01) and Vmin (p=0,0001 and 0,013) were associated with an increased mortality.
We conclude that 2DE, Doppler and 3DE measures of RV and RA dysfunction are significantly correlated with 6MWD, BNP, UA and HM irrespective of the PH etiology. Moreover, UA, 6MWD, 3D and 2D RA Vmax and Vmin were significantly associated with PH mortality.

P4935 | BEDSIDE
Measurement of right atrial maximal and minimal volumes: comparison of a semi-automatic algorithm of real-time 3D echocardiography with cardiac magnetic resonance imaging

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Introduction: Real-time full-volume 3D echocardiography (RT3DE) allows rapid measurement of atrial volume without making geometric assumptions. This method has recently been validated against cardiac magnetic resonance imaging (CMR) for the left atrium. However for right atrial (RA) volume 3DE has so far only been validated against CMR with reconstructed 3DE based on multiple 2D image planes. Our aim was to compare RA volume acquired by RT3DE and measured with a semi-automatic endocardial border detection algorithm with RA volume determined by CMR as reference method.
Method: 20 patients were studied RT3DE and CMR within 24h. RT3DE RA maximal (n=20) and minimal (n=18) volumes were measured using a semiautomatic border detection method. These volumes were compared with RA volume determined by CMR on a 1.5 T MRI from contiguous 4 chamber slices covering the whole heart using a 2D true-fisp cine MRI sequence.
Results: RA maximal volumes determined by RT3DE were smaller than CMR derived volumes. Linear regression analysis showed a rather good correlation between RA maximal volume determined by RT3DE with CMR derived volume (r^2=0.65). Correlation was better for RA minimal volume (r^2=0.85). Bland-Altman

Right atrium (RA)	Patients	Mean ± SD (range)
RT3DE RA maximal volume (ml)	n=20	36.8±24.7 (11.8–101.1)
CMR RA maximal volume (ml)	n=20	53.2±29.3 (21.1–121)
RT3DE RA minimal volume (ml)	n=18	21.1±17.9 (4.1–73.7)
CMR RA minimal volume (ml)	n=18	29.7±24.2 (8.2–95.3

analysis of CMR versus RT3DE RA maximal volume determination showed rather wide limits of agreement (-17.7 to 50.3 ml) with a moderate bias of 16.3±17.3 ml for CMRI volume. Limits of agreement and bias were smaller for RA minimal volume (-11.9 to 28.9 ml and 8.5±10.4 ml respectively).

Conclusion: This small preliminary study suggests that RA maximal volumes acquired by RT3DE and measured with a semiautomatic border detection method correlate well with CMR. However agreement between both methods was rather moderate with mean volume underestimation of RA maximal volume by RT3DE of 30.6% compared to CMR. Correlation and agreement was better for RA minimal volumes.

P4936 | BEDSIDE
Two and three dimensional echocardiographic assessment of respiratory variation on inferior vena cava size: who's the winner?

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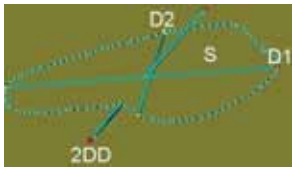
Accuracy in inferior vena cava (IVC) measurement has clinical implications in the diagnosis and management of cardiac disorders. Usually measured by transthoracic two-dimensional echocardiography (2D), the usefulness of three dimensional echocardiography (3D) has not been demonstrated in the evaluation of the IVC.

The aims of our study is to develop a methodology to explore the IVC by 3D and analyse the variation of IVC with respiratory motion in comparaison with 2D.

Twenty five patients underwent detailed transthoracic 2D and 3D assessment of IVC. 2D mesure of IVC diameter was performed according to the ASE guidelines developed in conjunction with the European Association of Echocardiography. 3D IVC was displayed according to its longitudinal axis from the junction with the RA. Then, cross-section of the VCI was positioned immediately after the junction with hepatic vein. The large and small diameter (D1 and D2) and the surface (S) of the section of the IVC were mesured. After deep breathing, re-adjustment of the section of the IVC and same measures were done. The IVC collapsibility index (IVCCI = IVCmax - IVCmin) / (IVCmax) wear calculate in 2D and for itch 3D parameter.

2DDmax and 2DDmin was respectively 21.5+3.1mm and 11.5+1.7mm (2D IVCCI = 46%). 3D shows that IVC in cross section has an oval geometric shape. D1max and D1min was 27.6+1.9mm and 22.3+1.5mm (D1 IVCCI = 19%). D2max and D2min was 15.6+1.2mm and 11.1+1.1mm (D2 IVCCI = 28%). S max and min was respectively 3.2+0.6cm^2 and 2.0+0.4cm^2 (S IVCCI = 37%). 2DD is less than D1 ($p<0.001$).



2D is not able to measure his maximal diameter IVC and to perform the exact IVC following during the respiration. 3D assessment of IVCT added more valuable information that may help in its management.

P4937 | SPOTLIGHT
Right atrial volumes with 3D and 2D echocardiography are better than inferior vena cava for estimation of elevated right atrial pressure in pulmonary hypertension

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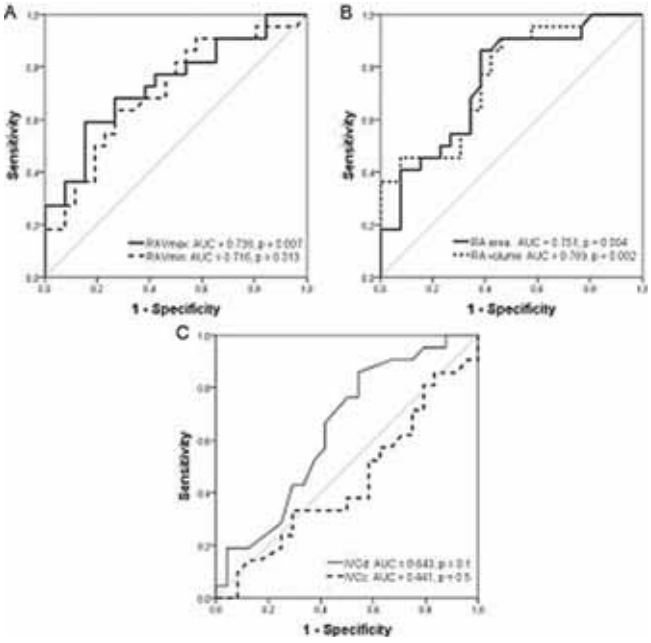
Purpose: To determine whether right atrial volumes (RAV) with 3D-echocardiography (3DE) can assess elevated mean right atrial pressure (mRAP) in patients evaluated for pulmonary hypertension (PH).

Background: PH is characterized by elevated pulmonary arterial pressure (PAP). Predictors of poor prognostic outcome are enlargement of the right atrium (RA) and elevated mRAP due to RV failure.

Methods: 52 patients (64±15 years, 54% women) evaluated for PH underwent right heart catheterization within 48 hours from 3DE. 7% were not feasible to visualize with 3DE. Maximum (RAVmax) and minum (RAVmin) volumes were measured with 3DE. mRAP was obtained from catheterization and >8 mmHg was considered elevated. Cine cardiac magnetic resonance (CMR) was used in 26 patients for comparison of 3DE RA measurements. Receiver-operating characteristics curves with area under the curve (AUC) were calculated.

Results: RAVmax and RAVmin correlated with mRAP (r=0.364 and r=0.304,$p<0.05$), and so did RA maximum volume with 2D-echocardiography (r=0.423,p=0.003). AUC was 0.736 for RAVmax, 0.716 for RAVmin and 0.769 for 2D RA volume to discriminate elevated mRAP ($p<0.05$ for both), with optimal 'threshold' point calculated to 57ml/m^2 for RAVmax, 30ml/m^2 for RAVmin and 36ml/m^2 for 2D RA volume. AUC was neither significant for inferior vena cava diameter nor collapsability for predicting mRAP>8mmHg (NS). Interobserver variability for 3DE was low, intraclass correlation coefficient was 0.923 for RAVmax and 0.918 for RAVmin. Bias between 3DE and the average of 3DE and CMR was -54±30% for RAVmax and -66±34% for RAVmin.



ROC analyses.

Conclusions: Enlarged right atrial volumes with 3DE or 2DE are markers for elevated mean right atrial pressure in PH-patients - while cava measurements are not - this despite large bias between CMR and 3DE.

P4938 | BEDSIDE
Assessment of tricuspid annulus shape and orientation using three-dimensional transesophageal echocardiography

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Background: The tricuspid annulus (TA) is a complex structure that has been rarely evaluated. Three-dimensional transesophageal echocardiography (3D-TEE) gives us the unique opportunity to evaluate TA shape and dimensions.

Methods: 3D dynamic volumetric datas of the TA were acquired by TEE using a matrix array transducer (X7-2t, Philips) in 184 patients. Multiplanar reconstructions were performed offline using a dedicated software (QLab7, Philips). Long-axis (LA) diameter, short-axis (SA) diameter and the area of the TA at the time of its maximal opening were measured. The eccentricity index (EI) of the TA was defined as LA/SA and TA orientation as the angle between the interatrial septum axis (aortic valve on the top at 0°) and the LA in the surgical view.

Results: Morphology of TA was more often oval (EI=1.35±0.22) but shapes were significantly different among indivuals, from circular to oval (EI values from 1 to 2.15). TA dilatation occurred homogeneously in all the directions of the right ventricle free wall as attested by the very good correlation between the TA area and both LA (r=0.89, $p<0.0001$) and SA (r=0.88, $p<0.0001$). TA dilatation, as shown by increase in TA area, was associated with a small decrease of EI (r=-0.21, $p<0.0001$), thus a trend to a more circular TA. All orientations of TA were observed, from 5 to 175° (mean=87°±57°) with a bimodal distribution (most frequently at 40° and 150°).

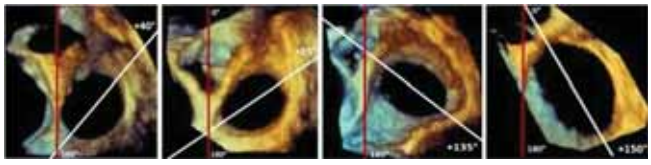

Figure 1

Conclusion: 3D-TEE allowed a good assessment of the TA shape and orientation, which is significantly different among individuals. This method could be interesting to improve assessment of TA dilatation before left-heart valve surgery.

BIOMARKERS AND DIAGNOSIS OF ACUTE CORONARY SYNDROME IN THE EMERGENCY DEPARTMENT

4958 | BEDSIDE
Incremental value of copeptin to high-sensitivity cardiac troponin T alone in the early diagnosis of acute myocardial infarction

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Purpose: Recently, two novel approaches have shown to improve the early diagnosis of acute myocardial infarction (AMI): high-sensitivity cardiac troponin (hs-cTn) and copeptin, a sensitive marker of endogenous stress. It is unknown, whether the combination of hs-cTn and copeptin would further increase diagnostic accuracy.
Methods: In a prospective, international multicenter diagnostic study, copeptin and high-sensitivity cardiac troponin T (hs-cTnT) were measured in 1991 patients presenting to the emergency department with acute chest pain. The final diagnosis was centrally adjudicated by two independent cardiologists blinded for the investigational biomarkers.
Results: AMI was the adjudicated final diagnosis in 429 (22%) patients. The diagnostic accuracy for measurements obtained at presentation, as quantified by the area under the receiver operating characteristic curve, did not differ significantly between the combination of hs-cTnT and copeptin (0.93; 95% confidence interval (CI) 0.92-0.94) as compared to hs-cTnT alone (0.93; 95% CI 0.92-0.94, p=0.076). The single use of hs-cTnT below the 99th percentile (14ng/l) resulted in a sensitivity of 90% and a negative predictive value of 97%. Using the dual marker strategy with copeptin resulted in a significant improvement with a sensitivity of 98% and a negative predictive value of 99% for hs-cTnT below the 99th percentile (14ng/l) and copeptin below 9pmol/l ($p<0.001$ for both comparisons).
Conclusions: The additional use of copeptin further improves the early rule-out of AMI in patients presenting with acute chest pain to the emergency department as compared to hs-cTnT alone. The additional use for the rule-in of AMI, however, seems limited.
Trial registration: ClinicalTrials.gov number, NCT00470587

4959 | BEDSIDE
Utility of absolute and relative kinetic changes of high-sensitivity troponin T for risk stratification in patients with and without acute coronary syndrome

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Purpose: We sought to evaluate the prognostic impact of absolute and relative kinetic changes of high-sensitivity cardiac Troponin T (hs-cTnT) in comparison to baseline hs-cTnT elevations for risk stratification in acute coronary syndrome (ACS) and non-ACS conditions with increased hs-cTnT.
Methods: hs-cTnT was measured serially in patients presenting with acute symptoms to our emergency department. We assessed the prognostic performance for mortality prediction of baseline and serial hs-cTnT concentrations in all consecutive patients with ACS (n=406) or hs-cTnT increases not due to ACS (n=442) within 3-6 h after admission.
Results: In ACS patients, receiver operating characteristics (ROC) revealed optimized cut-off values of 12.2 ng/L for absolute δ-change (AUC=0.66, $p<0.001$), 31.2 ng/L for baseline hs-cTnT (AUC=0.71, $p<0.001$) and 45.2 ng/L for maximal hs-cTnT (AUC=0.68, $p<0.001$). C-statistics showed superiority of absolute δ-changes (p=0.0003), baseline hs-cTnT (p=0.04) and maximal hs-cTnT (p=0.02) compared to relative δ-changes. However, the combination of baseline hs-cTnT values with either absolute or relative δ-changes did not improve risk prediction compared to baseline hs-cTnT alone (p=n.s.). Moreover, a significant incremental value in comparison to the 99th percentile cut-off for mortality prediction using net reclassification improvement was only observed for the ROC-optimized baseline hs-cTnT and the max. hs-cTnT, but not for hs-cTnT absolute or relative kinetic changes. In non-ACS conditions, the ROC-optimized cut-off value of 46.2 ng/L for baseline hs-cTnT (AUC=0.661, $p<0.001$) was superior to absolute (p=0.007) and relative δ-changes regarding prognostication (p=0.045). Similar to the logistic ROC analysis in the ACS cohort, the combination of baseline hs-cTnT values with absolute δ-changes (AUC=0.646) or relative δ-changes (AUC=0.609) revealed no significant difference in comparison to baseline hs-cTnT alone (p=n.s.).
Conclusions: Our data suggest that the magnitude of baseline hs-cTnT, and not acute dynamic changes, convey superior long-term prognostic information in ACS and non-ACS conditions. Moreover, absolute and relative kinetic δ-changes of hs-cTnT do not add significant incremental value for mortality prediction in both conditions.

4960 | BEDSIDE
Diagnostic utility of copeptin in addition to high-sensitivity cardiac troponin for the early diagnosis of non-ST-elevation acute coronary syndromes

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Aims: Rapid and reliable exclusion of NSTEMI during an Emergency Department (ED) triage is a major unmet clinical need. We aimed at verifying the non-inferiority of a single-sampling strategy of high-sensitivity cardiac troponin I (hs-cTnI) and copeptin compared with the dual hs-cTnI sampling for the early diagnosis of NSTEMI versus Non Coronary Chest Pain (NCCP) in a cohort of patients admitted at the ED.
Methods: Copeptin, hs-cTnI, CK-MB and myoglobin levels were measured at presentation in 196 consecutive patients admitted to the ED for non-traumatic chest pain with onset within the previous 6 hours and without ST elevation on a 12-lead electrocardiogram (ECG). The comparative diagnostic performance for NSTEMI diagnosis of a combination of hs-cTnI and copeptin, hs-cTnI and CK-MB, hs-cTnI and myoglobin on admission; and of the 3 hours hs-cTnI serial sampling was studied with reference to the adjudicated post-discharge diagnosis. The diagnostic accuracy and the predictive value of the various biomarkers combinations were assessed using both ROC curve and Net Reclassification Improvement (NRI) analysis. A margin to define non-inferiority between the areas under the ROC curves (AUC) was set at <0.05.
Results: The adjudicated final diagnosis of NSTEMI was done in 29 patients (14.8%). At the time of admission/first blood sampling analysis, a copeptin level <14 pmol/L in combination with a hs-cTnI <0.045 ng/mL safely ruled out NSTEMI with both a sensitivity and a negative predictive value of 100%. The combination of hs-cTnI and copeptin generated an AUC of 0.91 (95% CI: 0.88-0.94), which was non-inferior with respect to the 3-hours interval hs-cTnI serial sampling, with a trend towards improved diagnostic performance when compared with the 0.89 (95% CI: 0.81-0.97) for hs-cTnI alone, 0.86 (95% CI: 0.77-0.92) for hs-cTnI/CK-MB, and 0.83 (95% CI: 0.73-0.90) for hs-cTnI/myoglobin. When compared with hs-cTnI alone, the combination of hs-cTnI and copeptin yielded a significant positive NRI of 0.459 (p=0.043). Short-term (<3 months) follow-up of patients with normal copeptin and hs-cTnI serum levels on admission was completely uneventful (out-of-hospital major adverse cardiovascular event rate 0%).
Conclusions: The combined single-sampling use of copeptin and hs-cTnI is non-inferior to dual hs-cTnI sampling to allow a rapid and reliable ruling-out of NSTEMI in patients within 6 hours from chest pain onset. The diagnostic utility of single-sampling copeptin/hs-cTnI may result in a substantial cost-saving benefit compared with dual hs-cTnI sampling by reducing the total treatment cost of chest pain management in the ED.

4961 | BEDSIDE
High sensitivity troponin T serial changes as a gatekeeper for hospital admission and resources utilization

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Purpose: The use of high sensitivity cardiac Troponin T (hs-cTnT) assay might lead to overdiagnosis and overtreatment of Acute Myocardial Infarction (AMI), if compared with standard cardiac Troponin T (cTnT) test. This study aimed to assess the impact of introducing hs-cTnT serial measurements in the everyday clinical practice of an Emergency Department (ED) at a tertiary care teaching hospital.
Methods: We compared 597 consecutive patients presenting with suspected Acute Coronary Syndrome (ACS) at the ED during March 2010, when standard cTnT assay was used, and 629 consecutive patients admitted during March 2011, when hs-cTnT test was used.
The diagnosis of AMI using standard cTnT testing was made in the presence of at least one value of cTnT $>0{,}03$ μg/L. When hs-cTnT was used, the diagnosis of AMI was based on hs-cTnT serial changes (rise or fall) $\geq$50% or $\geq$20% depending on baseline values (14-52 or >52 ng/L respectively).
Results: The two study groups did not differ in terms of baseline characteristics. Patients with suspected ACS whose troponin levels were above the 99th percentile significantly increased when using the hs-cTnT assay (cTnT 17,4% vs. hs-cTnT 38,8%; $p<0{,}001$). Accordingly, also the mean GRACE risk score increased (124 vs. 135; $p<0{,}001$).
However, the final diagnosis of AMI did not change significantly (8,7% vs. 6,8%; p=0,26) by using the above-mentioned pattern of hs-cTnT. When looking at hs-cTnT tested patients, if we had used the 99th percentile as a cut-off for the diagnosis of AMI instead of the described serial changes, we would have observed an increase in the number of AMI diagnosis (6,8% vs. 9,9%; p=0,07). In particular, had we used the hs-cTnT cut-off value of 14 ng/L for the diagnosis of AMI (99th percentile), we would have observed a 50% increase of NSTEMI occur-

rence (5,7% vs. 8,7%; p=0,05), with a reciprocal decrease in the number of UA cases (4,9% vs. 1,9%; p=0,05).
In addition, no significant differences were found with respect to mortality (2,7% vs. 1,9%; p=0,37), hospitalization (60,0% vs. 56,2%; p=0,21) and use of coronary angiography (10,7% vs. 9,7%; p=0,55) between the two study groups.
Conclusions: We did not observe overdiagnosis and overtreatment issues in presenters with suspected ACS managed by appropriate changes in hs-cTnT levels, despite an increased rate of patients with abnormal troponin levels. This came without an increase in mortality and resources utilization.

4962 | BEDSIDE
Comparison of a high sensitive troponin T and a conventional troponin I assay for the early detection of myocardial injury

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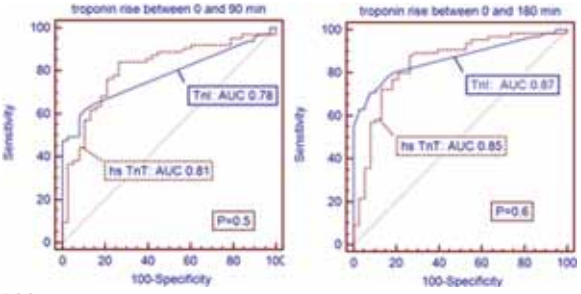
Purpose: More sensitive troponin assays have allowed to detect ischemia induced myocardial necrosis within 3h after onset of cardiac ischemia. The value of troponin assays for detecting myocardial injury (MI) in early (<2h) chest pain presenters is still a matter of debate.
Methods: The "early presenter" model was tested in 103 stable patients (76% male, age (median, interquartile range) 70 (63-77) years) in whom a short period of myocardial ischemia was induced during stenting of a significant coronary artery stenosis. Blood samples for high sensitive troponin T (hsTnT) and conventional troponin I (TnI) were taken at the start of the procedure and 90, 180 and 360 minutes after stent implantation. Myocardial injury was defined on the 90 and 180 min sample as an absolute rise of TnI or hsTnT >50% of the upper limit of normal. The final diagnosis of MI was made on the 360 min blood sample as an hsTnT >14 ng/l and a Trop I >45 ng/L and an absolute rise of >50% ULN.
Results: The final diagnosis of MI on the 360 min sample was made in 63% of the patients. MI at 90 min was demonstrated in 18,2% of patients with TnI and in 20, 9% for hsTnT. At 180 min MI was demonstrated for 27,3% of patients with TnI, and in 38,2% with hsTnT. The diagnostic value, expressed as the area under the curve (AUC) of hsTnT and TnI at 90 and 180 min samples are depicted in ROC curves. There was no significant difference in performance between both troponin assays.



ROC curves

Conclusions: In this early presenter model, both high sensitive troponin T and conventional troponin I assessment at 90 and 180 minutes after induced ischemia underestimate the presence of myocardial necrosis as established at 360 min. Our data suggest to apply a 6 h rather than a 3h troponin protocol in early (<2h) chest pain presenters.

4963 | BEDSIDE
Novel high sensitivity troponin assay requires higher cut-off value to separate acute coronary syndromes from non-acute coronary syndromes in a high risk population

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Purpose: The high sensitivity troponin T (hs-TnT) assay has not been validated to diagnose acute coronary syndrome (ACS) in high risk populations.
Methods: We retrospectively reviewed consecutive cardiology admissions who had 2 hs-TnT (Roche) measurements in the first 12 hours of presentation. Patients were grouped as ACS or non-ACS and the utility of the hs-TnT level and percent change was assessed.

Table 1. Diagnostic utility

hs-TnT	Sensitivity	Specificity	Accuracy
>14 ng/L	87.8%	24.7%	64.8%
>50 ng/L	74.3%	60.0%	69.1%
>75 ng/L	71.6%	75.3%	73.0%
>100 ng/L	68.9%	80.0%	73.0%
>20% rise/fall	62.8%	69.4%	65.3%
>30% rise/fall	56.8%	80.0%	65.2%
>50% rise/fall	43.2%	92.9%	61.4%

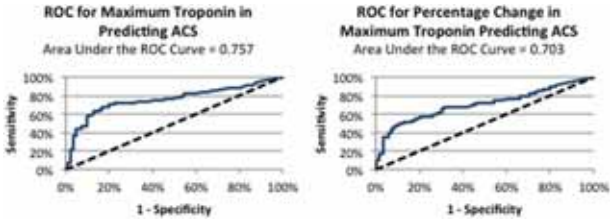

Figure 1. Receiver operator curves.

Results: There were 233 patients [67±12 years; 153 (66%) male] with ACS diagnosed in 148 (64%). The area under the ROC (fig.1) was higher for hs-TnT levels (0.757) than for percent change (0.703). The 99th percentile cut-off of 14 ng/L was sensitive but not specific, while a higher cut-off of 75 ng/L was more accurate (table 1). Percent change of hs-TnT was not more accurate.
Conclusion: In high-risk inpatients, a higher hs-TnT cut off was more accurate than the 99th percentile, but no value or was able to rule in and rule out ACS. Correlation to clinical judgment is essential.

4964 | BEDSIDE
Incremental value of a single resting ultrasensitive cardiac troponin I measurement to rule-out myocardial ischemia

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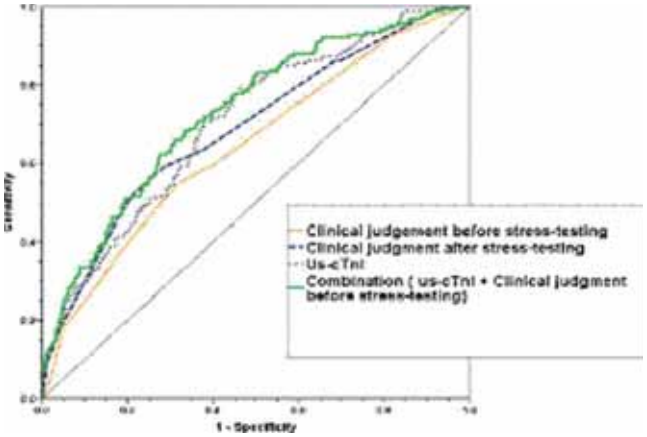
Background: The aim of this study was to investigate the value of a novel "ultrasensitive" cardiac troponin I (us-cTnI) measurement to rule-out exercise-induced myocardial ischemia (MIS) in patients without known coronary artery disease (CAD).
Methods: We included 714 patients without previously known CAD referred for rest/stress myocardial perfusion single photon emission tomography (SPECT). All clinical information available to the treating cardiologist was used to quantify the clinical judgment regarding the presence of MIS using a visual analogue scale twice: once prior and once after bicycle exercise stress-testing. Us-cTnI measurements were obtained before stress-testing in a blinded manner. The presence of MIS was adjudicated based on perfusion SPECT combined with coronary angiography findings.
Results: MIS was detected in 167 (23.4%) participants. Us-cTnI levels were significantly higher in patients with MIS (4.0 ng/l [95%CI 2.8-8.6] versus 2.6 ng/l [95%CI 1.8-4.1], p<0.001) and remained an independent predictor of ischemia in multivariable analysis (p<0.001). Combining clinical judgment prior to exercise testing with us-cTnI levels increased diagnostic accuracy as quantified by the area under the receiver-operating curve from 0.64 to 0.73 (p<0.001), which tended to be superior also to clinical judgment after exercise testing (0.69, p=0.056). A single resting us-cTnI measurement provided similar diagnostic accuracy as integrated clinical judgment after exercise testing including work load, as well as symptoms and ECG changes (0.70 versus 0.69, p=ns).



Conclusion: Us-cTnI measurements seem to complement non-invasive clinical assessment in the patients with suspected CAD.

4965 | BEDSIDE
Ischemia modified albumin is a new biomarker for early detection of myocardial injury in acute coronary syndromes

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Purpose: This study was designed to assess sensitivity & specificity of ischemia

modified albumin (IMA) as a new biochemical marker of early detection of myocardial injury in acute coronary syndromes.
Methods: This study included 76 patients, who presented to the emergency department (ED) with acute chest pain within 3h of pain onset and 10 people (matched for age, gender and risk factors) as a control group. The blood samples obtained from patients in the ED, and repeated 4-6 hours after admission to the coronary care unit (CCU) for those subsequently diagnosed with ACS by history, clinical examination, electrocardiogram (ECG) and cardiac markers. IMA level was detected by Albumin-Cobalt Binding (ACB) test, and receiver operating characteristic characteristic (ROC) curve was performed to detect the cut off value of IMA with best sensitivity and specificity in diagnosis of ACS.
Results: There was a higher IMA level in patients with ACS (5.27±4) compared to control group (1.7±0.8), p=0.007. The ROC curve showed that IMA level could be used to detect cases of myocardial injury in ACS at a level of 3.25u/ml, with 89.5% sensitivity and 100% specificity and 82% accuracy. On admission, there was a highly significant difference between IMA and troponin I (Tn I) test regarding sensitivity in STEMI (STEMI=88.5% vs 30.7%, p=0.001) and non ST-elevation myocardial infarction (NSTEMI=94.4% vs. 16.7%,p=0.001) patients. On the contrary,there was no significant difference between IMA on admision and cTnI at 4-6 hours after admission in STEMI (88.5% vs. 100%, p=0.633) and NSTEMI (94.4% vs. 100%, p=0.829) patients. Comparing changes in cTn I at 4-6 hours of admission to IMA results on admission revealed a highly significant difference in favour of IMA in detecting myocardial ischemia in patients with unstable angina (UA=87.5% vs. 0%, p<0,001),but both (IMA and TnI)had 100% specificity.
Conclusions: IMA is highly sensitive for the early diagnosis of ACS in patients presenting to ED within 3 hours of pain onset, compared to other cardiac markers as Troponin I. IMA may be a useful biomarker for the identification of UA patients presenting with typical acute chest pain and/or abnormal electrocardiograms with negative Tn I.

4966 | BEDSIDE
Optimal cutoff-value of a prototype high-sensitivity cardiac troponin I assay by Beckman-Coulter in patients with kidney disease for the early diagnosis of acute myocardial infarction

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Purpose: The recent introduction of high-sensitivity cardiac troponin (hs-cTn) assays improved the early diagnosis of acute myocardial infarction (AMI). However, its diagnostic utility has never been tested in patients with kidney disease (KD), who are known to have elevated levels of cTn already in the absence of AMI, which may lead to a lower diagnostic value of more sensitive cTn in this high-risk subgroup.
Methods: We conducted an international multicenter study to examine the diagnostic accuracy of a prototype hs-cTnI assay by Beckman-Coulter in 1155 patients presenting to the emergency department with symptoms suggestive of AMI, of whom 190 (16%) were determined to have KD (MDRD GFR <60ml/min/1.73m^2) and to derive the optimal cutoff value for the diagnosis of AMI in patients with KD. The final diagnosis was centrally adjudicated by two independent cardiologists based on hs-cTnT.
Results: AMI was the final diagnosis in 33% (n=63) of all KD-patients as compared to 17% in patients with normal kidney function (p<0.001). Among KD-patients with other diagnoses than AMI, baseline hs-cTnI-levels were elevated above the 99thpercentile in 54%, In patients with KD the diagnostic accuracy at presentation, quantified by the area under the receiver-operator-characteristic curve (AUC), was 0.89 (95%CI for AUC, 0.84-0.94). In patients presenting within three hours after the onset of chest pain, the AUC was 0.82 (95%CI 0.70-0.93). In KD, the optimal hs-cTnI cutoff derived from the ROC curve was 25.9ng/l compared to 11.1ng/l in patients with normal kidney function (official 99th percentile 9ng/l, provided by the manufacturer).
Conclusions: The investigated prototype hs-cTnI assay has a high diagnostic accuracy also in KD-patients. Mild elevations are common in non-AMI patients. However, the optimal cutoff-level in KD-patients seems to be about three times as high as the officially recommended cutoff.
ClinicalTrials.gov number, NCT00470587

4967 | BEDSIDE
Triple biomarker index added to the tropnin test improves laboratory diagnosis of acute coronary syndromes

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Background: Laboratory diagnosis of acute coronary syndromes (ACS) still remains a challenge. Cardiac troponins or myoglobin are highly sensitive to detect myocardial damage, but fail in ACS patients without myocardial necrosis. As a result of retrospective multimarker analysis, we have selected 3 biomarkers to test in a prospective study: Pregnancy Associated Plasma Protein A (PAPP-A), C-reactive protein (CRP) and haptoglobin (HPT), which reflect different pathophysiological aspects of ACS.
Aim: Prospectively evaluate diagnostic utility of the triple biomarker index (MultiHPC) derived from PAPP-A, CRP, and HPT blood concentrations added to the routine troponin I (TnI) evaluation in patients presented with suspected ACS.
Methods: Blood samples were obtained in 154 patients (mean age 62.7±11.3 y, 89 females) admitted consecutively to the EU department either after prolonged anginal episode or with the newly developed or worsening angina. Initial ACS diagnosis was based on ESC guidelines clinical criteria. Further diagnosis verification was done according to the in-hospital examination and 4 weeks follow-up. Triple biomarker index MultiHPC was derived as a sum of Log12[PAPP-A]+LOG4[CRP]+LOG1.42 (e powered by [HPT]) with the threshold value >3.
Results: After in-hospital examination and follow-up evaluation, ACS at admission was considered in 59 patients: according to the TnI test, 17 TnI-positive patients were referred as "true-positive", 42 TnI-negative patients were "false-negative". Other 95 patients had stable coronary artery disease (SCAD) and were TnI-negative (95 "true negative" and zero "false positive"). Thirty-two TnI-negative patients with ACS and 18 patients with SCAD had MultiHPC>3. When the MultiHPC criterion was added to the TnI, the net reclassification improvement (NRI) was 0.353 (p<0.001).
Conclusion: Addition of Triple biomarker index MultiHPC to the routine TnI test improved laboratory diagnosis of ACS significantly for a net of 35 per cent by increase in sensitivity and slight loss of specificity.

PERCUTANEOUS CORONARY INTERVENTION OUTCOMES: THINK LONG-TERM

4973 | BEDSIDE
The mode of dual antiplatelet therapy cessation is directly associated with adverse events even with 2nd generation DES: Insights from the PARIS registry

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Background: The risk of adverse outcome after stopping dual anti-platelet therapy (DAPT) in patients who have undergone percutaneous coronary intervention (PCI) is dependent on the context of treatment cessation. Whether these associations persist among unselected real-world patients after 2nd generation DES implantation remains unknown.
Methods: The PARIS (Patterns of non-adherence to Anti-platelet Regimens In Stented patients) registry was an observational multinational study of 5018 patients undergoing PCI with stenting, of whom 3533 (70.4%) received a 2nd generation DES. Cessation was categorized into physician-recommended discontinuation, brief interruption for surgery or disruption (due to non-compliance or bleeding). Associations between DAPT cessation and adverse events among patients who received 2nd generation DES were examined using Cox regression with DAPT cessation modeled as a time-updated covariate.
Results: Over 2 years follow-up, 48% of patients remained on DAPT. Rates of discontinuation, interruption and disruption were 31%, 8% and 13%, respectively. Most MACE events (n=195) occurred while patients were on (n=149, 76.4%) rather than off (n=46, 23.6%) DAPT. Patients who disrupted DAPT were more often female, current smokers and more likely to present with ACS. Compared to those remaining on DAPT, disruption was associated with a 2-fold increased risk for ST while no ST occurred after interruption or discontinuation (Table). Patients who interrupted DAPT (<5 days) for surgery did not have higher rates of thrombotic MACE compared to patients on-DAPT.

	On DAPT (N=1704)	Discontinuation (N=1092)	Interruption (N=284)	Disruption (N=453)
Cardiac death	1.0 (ref)	0.52 (0.21–1.29)	0.80 (0.25–2.61)	1.63 (0.86–3.11)
Probable or definite ST	1.0 (ref)	N/A	N/A	2.10 (0.69–6.43)
Spontaneous MI	1.0 (ref)	0.73 (0.32–1.68)	1.72 (0.73–4.07)	2.75 (1.64–4.61)
MACE	1.0 (ref)	0.60 (0.32–1.13)	1.18 (0.57–2.46)	1.91 (1.23–2.95)

DAPT: dual antiplatelet therapy; ST: stent thrombosis; MI: myocardial infarction; MACE: cardiac death, ST, or MI.

Conclusion: Among unselected patients receiving 2nd generation DES, the impact of DAPT cessation on cardiac risk varies by mode and is modest overall with most events occurring among those on DAPT. DAPT is continued in almost half of patients, despite the safety seen for physician recommended discontinuation and brief interruption for surgery.

4974 | BEDSIDE

Impact of diabetes on clinical outcomes among women undergoing percutaneous coronary interventions with drug-eluting stents: a patient-level pooled analysis of 26 randomized trials

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Purpose: To evaluate the impact of diabetes mellitus (DM) on clinical outcomes among women with coronary artery disease undergoing percutaneous coronary interventions (PCI) with drug-eluting stents (DES).
Methods: We pooled patient-level data of 10,448 women undergoing PCI with DES from 26 randomized trials. Baseline characteristics and long-term clinical outcomes were stratified according to diabetes status at baseline. Associations between DM and outcomes were examined using Cox regression with trial entered as a random effect. The primary outcome was the composite of all-cause death and myocardial infarction (MI). Secondary outcomes were target-lesion revascularization (TLR), and definite or probable stent thrombosis (ST).
Results: Out of 10,448 women treated with DES, 3,294 (31.5%) had DM at baseline. Mean age was 67.2±10.6 with no differences according to diabetes status. Women with diabetes presented more frequently with stable CAD (60.9% vs. 54.4%, P<0.001) and had more comorbidities compared to non-diabetics. At 3 years follow-up, women with diabetes had higher risks of death or MI (12.6% vs. 8.7%; adjHR 1.51, 95%CI 1.27-1.80), death (7.9% vs. 4.5%; adjHR 1.86, 95%CI 1.07-1.10), MI (6.3% vs. 4.8%; adjHR 1.41, 95%CI 1.11-1.77), ST (2.5% vs. 1.2%; adjHR 2.19, 95%CI 1.43-3.36), and TLR (9.0% vs. 6.0%; adjHR 1.50, 95%CI 1.21-1.86) compared to women without diabetes (Fig. 1).

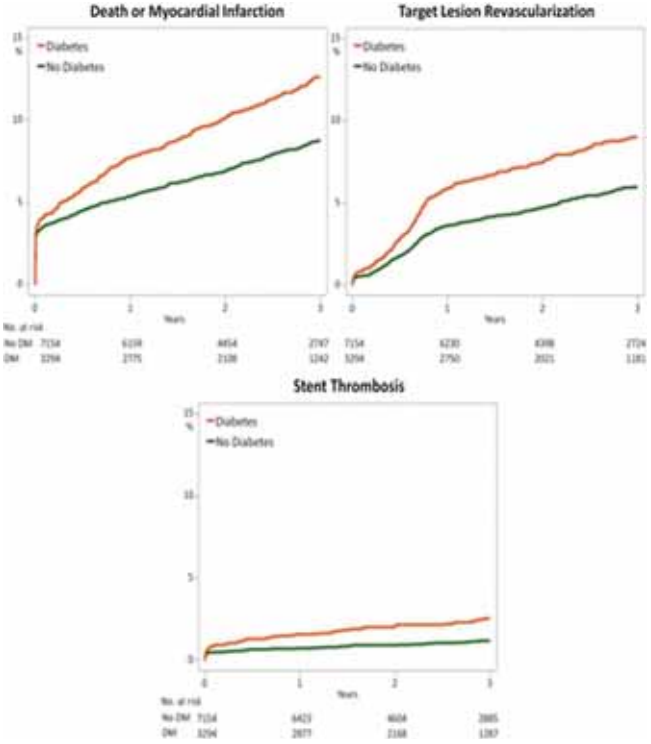

Figure 1

Conclusions: Women with diabetes undergoing PCI present more frequently with stable CAD than acute coronary syndromes and have a higher risk profile compared with women without diabetes. DM is associated with an increased risk of mortality and adverse ischemic events in women with coronary artery disease undergoing PCI with DES during long-term follow-up.

4975 | BEDSIDE

Lower 5-year event rates in the endothelial progenitor cell capturing stent compared with a drug eluting stent in de novo high-risk of restenosis coronary artery lesions; a randomized trial

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Aim: To evaluate the first long-term randomized adjudicated data regarding the safety and efficacy of the bio-engineered endothelial progenitor cell capturing stent (ECS) versus a drug eluting stent (DES).
Methods: In this prospective randomized pilot study, patients with de novo coronary artery lesions carrying a high risk of restenosis (chronic total occlusion, lesion length>23 mm, vessel diameter<2.8 mm, any lesion in a diabetic patient) were randomized to the ECS versus a DES (paclitaxel). Dual antiplatelet therapy (DAPT) was prescribed for ≥1 month in ECS and ≥6 months in DES. The primary endpoint is target vessel failure (TVF) at 5 years, a composite of cardiac death, myocardial infarction (MI) and target vessel revascularization, adjudicated by a clinical event committee. Clinical event rates were estimated by Kaplan-Meier method and compared with a log-rank test.
Results: A total of 193 patients were included with complete follow-up in 97% of the subjects. The primary endpoint of TVF was similar at 5 years with 23.8% in ECS vs 29.5% in DES (p=0.55) (fig 1). Between year two and year five the event rate is 4.1% in ECS vs. 17.2% in DES (p=0.011) (fig 2). DAPT cessation before 6 months after PCI was no independent predictor for the primary endpoint. The composite of death and MI was 6.3% in ECS vs 12.0% in DES (p=0.19). Definite stent thrombosis was observed in 4 cases in DES versus non in ECS.

Figure 1. Kaplan Meier survival estimates Target Vessel Failure

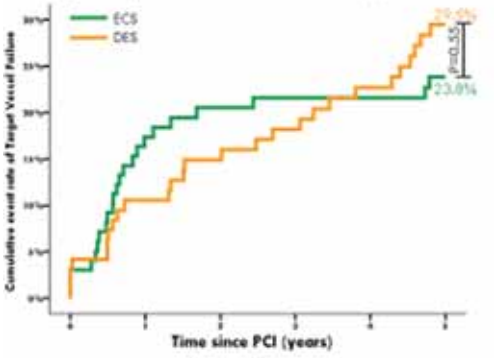
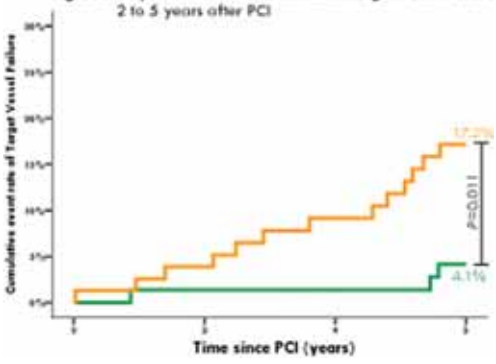


Figure 2. Kaplan Meier survival estimates Target Vessel Failure 2 to 5 years after PCI



TVF 0-5 years & 2-5 years.

Conclusions: The first randomized and adjudicated long-term results of the ECS versus a DES at 5 years show comparable performance and safety. Between two and five years a significant higher event rate was observed in the DES group compared with the ECS group. Importantly, no definite stent thrombosis was observed in the ECS treated group, compared with four cases in the DES group.

4976 | BEDSIDE

Long-term clinical outcomes after everolimus- and sirolimus-eluting coronary stents implantation: final 3-year follow-up of the reset

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Background: Long-term clinical outcomes of everolimus-eluting stent (EES) compared with sirolimus-eluting stent (SES) have not been fully evaluated yet, especially whether EES implantation could positively affect late adverse events reported after SES implantation occurring beyond 1 year.
Methods and results: In this all-comer prospective multicenter randomized open-label trial, 3196 patients were randomly assigned to implant either EES (N=1596) or SES (N=1600). At 3-year, EES was non-inferior to SES regarding the primary safety endpoint (all-cause death or myocardial infarction [MI]) (10.1% versus 11.5%, P non-inferiority<0.001, and P superiority=0.19). Cumulative incidence of definite stent thrombosis (ST) was very low and was not different be-

tween the 2 groups (0.5% versus 0.6%, P=0.81). There was no significant difference in the efficacy endpoint of target-lesion revascularization (TLR) between the EES and SES groups (6.6% versus 7.9%, P=0.16). However, the cumulative incidence of target-lesion failure (TLF: cardiac death/target-vessel MI/ischemia-driven TLR) was significantly lower in the EES group than in the SES group (8.8% versus 11.4%, P=0.01). By a landmark analysis at 1-year, the cumulative incidence of very late ST and late TLR were not different between the 2 groups (0.2% versus 0.2%, P=0.99, and 2.2% versus 2.9%, P=0.21, respectively).
Conclusions: The efficacy and safety outcomes for this trial after EES implantation remained comparable to those after SES implantation through 3-year follow-up. However, improvement of clinical outcome after EES implantation compared with SES implantation was suggested by the significantly lower cumulative incidences of TLF, which has been the most widely utilized primary endpoint in the stent-versus-stent trials.

4977 | BEDSIDE
Long term follow-up of lesions with fractional flow reserve > 0.80: 10 year follow-up of patients treated with revascularization according to FFR

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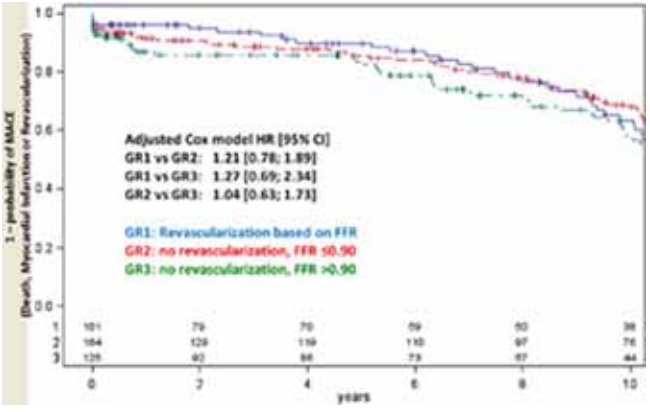
Aim: Fractional Flow Reserve (FFR) assessment is recommended to judge the need for revascularization of coronary stenosis when no ischemia had been demonstrated. The aim of this study was to investigate 10 year outcomes of patients left without revascularization.
Methods: From January 2000 to October 2003, 407 patients (452 coronary stenoses) were routinely submitted to FFR assessment. Based on FFR results, 136 (33%) underwent revascularization and 271 were left under optimal medical treatment alone. Follow-up was performed at 10 years for Major Adverse Cardiovascular Event (MACE), defined as death, acute coronary syndrome or revascularization. Three groups were defined: gr1 with FFR<0.80 and immediate revascularization, gr2 without revascularization and FFR between 0.80 and 0.90; and gr3 without revascularization and FFR>0.90. Outcomes were compared across groups with the adjusted Cox model. Analyses were repeated by lesions for acute coronary syndrome and revascularization.
Results: 10 year follow-up was available for 391 patients (96%): 53 (13.6%) patients died, 31 (8%) had an ACS and 136 (35%) had a MACE. By adjusted Cox model, there was no difference in survival, ACS or MACE-free survival across groups (figure). Analyses by lesion showed no impact of lesion severity according to angiography, or according to FFR on long term acute events or revascularization.



Conclusions: Under optimal medical treatment, patients with angiographic stenosis who are not submitted to revascularization for coronary stenosis based on FFR, have no excess of MACE or need for revascularization after 10 years as compared with those treated by revascularization. Neither angiographic percent stenosis nor FFR value were predictors of events.

4978 | BEDSIDE
Comparison of multivessel revascularization versus culprit vessel revascularization during primary percutaneous coronary intervention in patients with STEMI and cardiogenic shock

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Purpose: Current guidelines recommend multivessel (MV) revascularization during primary percutaneous coronary intervention (PCI) in patients with ST elevation myocardial infarction (STEMI) and hemodynamic instability. However, the evidence for MV revascularization in cardiogenic shock is not enough. We compared the clinical outcomes of MV revascularization with those of culprit vessel (CV) revascularization at the time of primary PCI in patients with STEMI and cardiogenic shock.
Methods: A total of 1,106 eligible patients with STEMI and cardiogenic shock were derived from the Korea Working Group on Myocardial Infarction registry. Cardiogenic shock was defined as systolic blood pressure ≤90 mmHg and the composite of major adverse clinical outcomes (MACE) as death, myocardial infarction (MI), or revascularization.
Results: Of the 1,106 patients, MV revascularization was performed in 225 (19.5%) patients and CV revascularization in 881 (80.5%) patients. There was no difference in clinical, angiographic, and procedural characteristics between both groups, except more diabetes in MV revascularization group (30.3 vs. 20.1%, p=0.015). In-hospital mortality was not different in MV versus CV revascularization groups (13.9 vs. 17.1%, p=0.393). The composite of MACE at 12 months was not different in both groups (27.7 vs. 29.2%, p=0.754). Death, MI, or revascularization at 12 months were also not different in both groups. In multivariable analysis, MV revascularization was not associated with decreased risk of in-hospital mortality (HR 0.89, CI 0.39-2.02, p=0.795) and the composite of MACE at 12 months (HR 1.01, CI 0.46-2.19, p=0.986).
Conclusions: This study showed that MV revascularization was performed at the time of primary PCI in approximately one fifth of patients with STEMI and cardiogenic shock and was not associated with decreased risk of in-hospital mortality and adverse clinical outcomes at 12 months when compared to CV revascularization.

4979 | BEDSIDE
Effect of transient vs permenant no-reflow on long term mortality in patients undergoing primary angioplasty

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Aim: Development of no-reflow (final TIMI <3 flow) in patients undergoing primary angioplasty is associated with increased mortality. However, affects of reversal of no-reflow with intracoronary medication (transient) or affects of persistance of no-reflow despite intracoronary medication (permanent) on long-term mortality are not clear. In this study we sought to determine the affects of transient (TIMI 3 flow after intracoronary medication) and permanent (TIMI flow <3 despite intarcoronary medication) no-reflow on long-term mortality.
Study design: 2993 patients (mean age 58.3, 675 female) undergone primary angioplasty for acute ST elevation myocardial infarction within first 12 minutes of pain without pretreatment with thrombolytics between 2006 January and 2010 February were investigated. 294 patients had post-procedural final TIMI <3 (no-reflow). 188 of those 294 no-reflow patients who had TIMI 3 flow after intracoronary medication (adenosin, ca channel blokers, nitroglyserin, glycoprotein 2b/3a receptor blocker) accepted as transient no-reflow group. 106 of those 294 no-reflow patients who had TIMI flow <3 despite intracoronary medication constituted permanent no-reflow group. 2699 patients without no-reflow created control group.
Results: Patients in permenant no-reflow group were older and mostly diabetic. Pain to door time was longer and Killip class at presentation was higher significantly in permanent no-reflow group. Angiographic thrombus burden was higher and, cut-off occlusion pattern and proximal lesions were more common in permanent no-reflow group. Presence of pre-procedural TIMI 2/3 flow was significantly lower in permanent no-reflow group. In-hospital mortality was meaningfully higher in permanent no-reflow group (12.3% vs 10.6% vs 3.0%, p<0.001 respectively). However, when only no-reflow groups compared, in-hospital mortality did not differ between no-reflow groups (permanent vs transient 12.3% vs 10.6%, p=0.672). On long-term follow up (median follow-up time 54 months) mortality was significantly higher both in permanent and transient no-reflow groups when compared to controls. (34.9% vs 29.3% vs 12.5%, p<0.001 respectively). Long term mortality was non significantly higher in permanent no-reflow group when compared to transient no-reflow group (34.9% vs 29.3%, p=0.316).
Conclusion: Development of no-reflow in the managament of STEMI was closely related to in hospital and long term mortality. Nevertheless, reversal of reflow after no-reflow development do not positively affect survival.

4980 | BEDSIDE
IVUS findings and clinical outcomes of angiographic late and very-late definite stent thrombosis treated with additional stent implantation versus balloon angioplasty

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Background: Although rare, late and very-late stent thrombosis (ST) are increasingly seen in daily practice due to the persistent risk of thrombosis late after implantation. Most cases present as ST elevation myocardial infarction (STEMI) and undergo urgent percutaneous coronary intervention (PCI). It is uncertain what is

the best invasive strategy for this condition. Intravascular ultrasound (IVUS) can guide PCI. We aimed to describe the IVUS findings of ST and to compare the clinical outcomes between patients treated with additional stent implantation vs. balloon angioplasty (POBA).
Methods: Multicenter registry including all consecutive patients with late or very-late ST undergoing IVUS-guided PCI in 5 institutions in 2009-13. The operator was left to decide the PCI strategy according to IVUS findings. IVUS were later analysed by 2 analysts, who performed a qualitative analysis of the images at baseline and after intervention. 4 items were recorded: late incomplete stent apposition (LISA), aneurysm, stent underexpansion and excessive neointimal proliferation.
Results: 86 patients included, 35 (40.7%) were diabetic, 49 (57.0%) of the ST were of drug-eluting stents (57.0%). The median (inter-quartile range, IQR) of the time after stent implantation was 3.5 years (1.1-5.7). The clinical presentation of the ST was STEMI in 72 (83.8%). 47 (54.7%) received an additional stent.
Prior to intervention, there were no differences in the presence of LISA (74.4% vs. 70.2%; p=0.67), aneurysm (10.3% vs. 12.8%; p=0.72), stent underexpansion (20.5% vs. 14.9%; p=0.49) and excessive neointimal proliferation (5.1% vs. 10.6%; p=0.35) between patients treated with POBA vs additional stent implantation. After PCI, LISA was still observed in 33.3% of patients treated with POBA and 56.1% of patients treated with additional stent (p=0.08). Persistent stent underexpansion was observed in 10.0% and 7.3% of patients (p=0.67), respectively. Clinical follow-up was obtained from 83 patients at a median (IQR) of 2.0 years (1.1-3.3). Cardiac death was observed in 0% vs. 7.3% of patients treated without and with additional stent implantation (p=0.11), respectively. Definite or probable new ST was observed in 0% vs. 7.5% of patients (p=0.10), respectively.
Conclusions: The most frequent IVUS findings in late and very-late ST were LISA and stent underexpansion. A simple strategy with POBA seems to improve the correction of LISA with respect to additional stent implantation. Although further investigations are required, additional stent implantation is associated with a trend towards worse outcomes at follow-up.

4981 | BEDSIDE
long-Term ischemic and bleeding outcomes after primary percutaneous coronary intervention for ST-elevation myocardial infarction in the very elderly (80+ years)

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Purpose: Uncertainty exists about the appropriateness of primary percutaneous coronary intervention (pPCI) in the very elderly using pharmacologic and invasive therapies that have undergone clinical testing primarily in younger patients. We investigated long-term ischemic and bleeding outcomes after pPCI in ST-elevation myocardial infarction (STEMI) patients aged ≥80 years.
Methods: Patients undergoing pPCI in a large tertiary referral hospital between 2003 and 2008 were included and subdivided in 3 age groups: <60, 60-79, and ≥80 years. Endpoints at 3-year follow-up included all-cause mortality, MACE (a composite of cardiac mortality, recurrent myocardial infarction, target lesion revascularization), and bleeding (BARC bleeding ≥3). Multivariable Cox Regression models were constructed.
Results: A total of 2002 STEMI patients were included, 885 (44.2%) aged <60, 921 (46.0%) 60-79, and 196 (9.7%) ≥80 years. The median follow-up duration was 4.9 years (IQR 3.4-6.4 years). Co-morbidities such as diabetes mellitus, prior stroke, malignant disease, anemia, and chronic kidney disease were more prevalent in the very elderly. Three-year mortality, MACE and bleeding rates are shown in figure 1. Age ≥80 years was an independent predictor of mortality (HR 3.1, 95% CI 2.1-4.7, p<0.001), and a borderline non-significant predictor of overall bleeding (HR 1.15, 95% CI 1.04-1.26, p=0.088), and a significant predictor of non-access site bleeding (HR 2.26, 95% CI 1.46-3.51, p<0.001).

Three year clinical outcomes

	Patients aged <60 years	Patients aged 60–79 years	Patients aged ≥80 years
Major adverse cardiac events	117/885 (20.3%)	301/921 (33.1%)	97/196 (50.3%)
Death	59/885 (6.7%)	181/921 (19.7%)	81/196 (41.3%)
Cardiac	50/885 (5.7%)	134/921 (14.8%)	67/196 (34.9%)
Recurrent myocardial infarction	87/885 (10.4%)	109/921 (13.3%)	35/196 (22.7%)
BARC ≥3 bleeding	115/885 (13.1%)	200/921 (22.4%)	67/196 (36.9%)
Non-access site related	57/885 (6.6%)	118/921 (13.4%)	37/196 (21.2%)

Conclusions: Rates of both ischemic and bleeding events increased with age, with very high event rates in the very elderly. Strategies aimed at tailored pharmaco-invasive therapy for the very elderly to reduce bleeding and optimize control of co-morbidities may improve clinical outcomes in the elderly.

CLINICAL CHALLENGES IN TRANSCATHETER AORTIC VALVE IMPLANTATION

4982 | BEDSIDE
Short and mid term comparative effectiveness of TAVR vs SAVR in a real world setting: results from the Italian OBSERVANT Study

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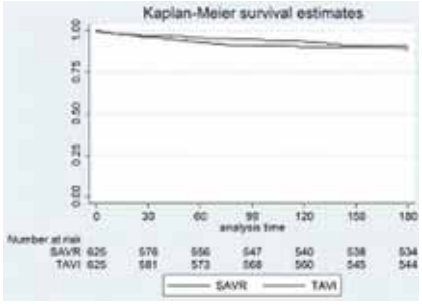
Purpose: To describe acute clinical outcomes of a large series of propensity-matched patients at low/intermediate risk undergoing transfemoral TAVR and surgical aortic valve replacement (SAVR).
Methods: OBSERVANT is an observational prospective multicenter cohort study, enrolling patients with severe aortic stenosis (AS) undergoing SAVR or TAVR. Propensity score method was applied to select two groups with similar baseline characteristics.
Results: The enrolled population included 5,864 SAVR and 1,935 TAVR patients. Matched population comprised 1300 patients (650 patients for each group) with a relatively low risk profile (log-EuroSCORE: 10.2±9.2% vs. 9.5±7.1%, SAVR vs. TAVR; p=0.104). A higher incidence of renal failure occurred in the SAVR group (10.9% vs. 6.1%; p=0.04) whereas a higher incidence of residual aortic regurgitation (50.6% vs. 9.5%; p<0.001), major access site complications (7.9% vs. 0.5%; p<0.001) and permanent pacemaker implantation (15.5% vs. 3.6%; p<0.001) occurred in the TAVR group. Thirty-day mortality was 3.8% and 3.2% (SAVR vs. TAVR; p=0.546). Six-months mortality was 10.4% and 8.8% (HR=0.87; p=0.450).



Six months mortality rates.

Conclusions: Transfemoral TAVR and SAVR have comparable 30-day and 6-month mortality in low/intermediate risk patients with AS. SAVR was associated with a higher peri-procedural risk of renal failure and TAVR with a higher peri-procedural risk of residual aortic regurgitation, vascular damage, and permanent pacemaker requirement.

4983 | BEDSIDE
Transcatheter aortic valve implantation in bicuspid aortic valve stenosis

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Purpose: Bicuspid aortic valve (BAV) stenosis is considered to be a relative contraindication to transcatheter aortic valve implantation (TAVI). We evaluated the TAVI outcomes in patients with BAV stenosis in a multinational registry.
Methods: Clinical characteristics, procedural data and outcomes were analysed in all patients with BAV stenosis at 12 international high-volume TAVI centres. Outcomes were assessed according to the Valve Academic Research Consortium criteria.
Results: The BAV registry includes 141 patients undergoing TAVI for BAV stenosis (64.3%), regurgitation (0.7%), or mixed stenosis/regurgitation (34.3%). The mean age was 77.7±9.1 years, 66% were male, and the mean logistic EuroSCORE and STS mortality risk score were 14.6±10.6% and 4.9±3.4%, respectively. BAVs were classified as Type 0 (24.4%); Type 1 (65.6%); and Type 2 (4.6%). The Edwards SAPIEN (n=51) and Medtronic CoreValve (n=91) were both implanted. The implanted THV diameters were: 23 mm (7.0%), 26 mm (36.4%), 29 mm (42.7%), and 31 mm (14.0%).
Major vascular complications were noted in 6.3%, device malposition in 6.3%, and 3.5% required implantation of a second THV during the index procedure. Overall procedural success was determined in 89.5% of patients. The mean post procedural transvalvular gradient was 11.5±9.8 mmHg and aortic regurgitation ≥ grade 2 occurred in 28.3% of cases. At 30-day follow-up, all-cause mortality or stroke occurred in 7.7% and 1.4%, respectively. A VARC device safety endpoint occurred in 22.4% and VARC efficacy was adjudicated in 83.9%.
Conclusions: TAVI for BAV disease is both feasible and safe, though post-implantation aortic regurgitation ≥ grade 2 occurs more frequently than reported

with tricuspid aortic valve stenosis. Further follow-up is required to determine the clinical efficacy in these patients.

4984 | BEDSIDE
Incidence and clinical impact of stroke complicating transcatheter aortic valve implantations (TAVI). Results of the German TAVI Registry

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Background: Transcatheter aortic valve implantation (TAVI) has emerged as a safe and effective treatment option for patients with severe, symptomatic aortic valve stenosis at high surgical risk. However TAVI still is an invasive procedure usually performed in a frail population, carrying a substantial risk for vascular complications, like stroke, which is known as a serious complication of transvascular interventions like PCI. At present only sparse data exist on the incidence and clinical risk factors of stroke complicating TAVI in clinical practice today.
Methods: We analysed data of the prospective, multicenter German TAVI Registry, which operated from January 2009 until June 2010.
Results: 1413 TAVIs were performed between 01/2009 and 06/2010. Stroke occurred in 3.1% of all patients undergoing TAVI. Patients with stroke showed significantly increased mortality rates at hospital discharge and at 30-day-follow up compared to patients without stroke. Multivariate analysis showed prior stroke and renal impairment as the only independent predictors for stroke complicating TAVI. Table 1 shows patient's characteristics, procedural details and clinical outcome.

Table 1

	Stroke (3.1%, 45/1413)	No stroke (95.5%, 1368/1413)	p-value
Age	80.9±6.5	81.8±6.2	0.21
Euro-Score	22±12	20±13	0.31
Peripheral arterial disease	44.4%	30.2%	<0.05
Prior stroke (ischemic or bleeding)	20.0%	7.4%	<0.01
Renal impairment	77.8%	59.9%	<0.05
Core valve prothesis implanted	82.2%	81.9%	0.96
Edwards Sapien prosthesis implanted	17.8%	18.0%	0.97
Atrial fibrillation at discharge	32.5%	19.9%	0.05
Clinical events			
In-hospital death	28.9%	6.9%	<0.01
Death rate (30-day FU)	35.6%	6.8%	<0.01
Discharge to nursing home	8.9%	0.6%	<0.01

Conclusions: Stroke complicating TAVI is a rare but serious complication in clinical practice leading to a five-fold increase in 30-day mortality rate, as well as a significant increase in morbidity and disability of patients, who survive this complication.

4985 | BEDSIDE
Mobile aortic valve deposits - a risk factor for periprocedural stroke during transfemoral TAVI?

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Purpose: Periprocedural stroke during transcatheter aortic valve implantation (TAVI) is a feared complication. Cerebral protection devices have been designed, but current preliminary data do not appear to justify their routine use. For their specific use, patients with an increased stroke risk must be identified, and intuitively aortic valve morphology, especially the presence of mobile deposits, may play a role.
Methods: Preinterventional transoesophageal echocardiographic (TEE) images were retrospectively analyzed for the presence of mobile deposits on the calcified aortic valve, which could potentially embolize as a result of procedural manipulation. Aortic valves were analyzed in mid-oesophageal short- and long-axis views. Patients with stroke during transfemoral TAVI were compared to patients without stroke.
Results: 11 out of 288 consecutive TAVI-patients (age 81±6 years; log EuroScore 20.4±11.9) had a stroke (3,8%) and neuroimaging suggested periprocedural cerebral embolization (Fig.1 A,B). These patients had a higher rate of mobile deposits than those without stroke (64% vs. 5%). Mobile deposits were visualized in either one view (+stroke:36%, -stroke:4%) or even both views (+stroke:27%; -stroke:1%) (Fig.1 C,D). Deposits were more often visible in long- than in short-axis view.
Conclusion: Retrospective analysis of TEE revealed a high rate of mobile deposits on the calcified aortic valve in patients with stroke in contrast to those without, suggesting such mobile deposits as a potential source for stroke. Although this hypothesis-generating observation needs to be confirmed in a larger, prospective cohort, it has important clinical ramifications. Patients with mobile deposits may benefit from the use of cerebral protection devices during TAVI.

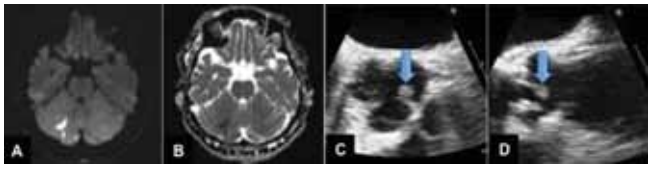

Figure 1

4986 | BEDSIDE
Impact of pre-existing atrial fibrillation on prognosis after transcatheter aortic valve implantation

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Objectives: Artrial fibrillation (Af) is highly prevalent in the elderly population around the world and significant predictors of cardiovascular events/death. Although many studies revealed that new-onset Af following TAVI is associated with poor outcomes, the predictive-value of pre-existing Af has not been thoroughly investigated in a large-cohort of TAVI-patients. The aim of our study was to determine the impact of pre-existing Af on clinical outcome after TAVI in a real-world setting.
Methods: Data were analyzed for 3051 patients (mean logistic-EuroSCORE: 21.9±14.3,) enrolled French-national-TAVI-registry, FRANCE2.
Findings: Of the 3051 patients (mean age: 82.8±7.1years) with TAVI, 820 (26.9%) had pre-existing Af. Compared with patients without Af, patients with Af had a significantly higher 30-day mortality and cumulative 1-year mortality rates (8.3% vs. 11.5%, P=0.007, 14.6% vs. 23.3%, p<0.001, respectively). After adjustment for considerable influential confounders in COX-regression multivariate model, Af was not associated with an increased risk of 30-day mortality, but independently associated with 1-year mortality (HR: 1.23; 95%CI: 0.96-1.59; p=0.104, HR: 1.50; 95%CI: 1.25-1.80; p<0.001, respectively), when compared to non-Af.
Conclusion: In this real-world TAVI registry, patients with pre-existing Af had a significantly worse survival outcome compared to patients without pre-existing Af. Pre-existing Af plays a crucial role in the selection process and is one of the major independent predictors of outcome after TAVI.

4987 | BEDSIDE
Impact of reduced left ventricular ejection fraction on mid-term mortality after transcatheter aortic valve implantation

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Purpose: Whether patients with reduced left ventricular function present worse outcome after transcatheter aortic valve implantation (TAVI) is controversial. The aim of this study was assess the impact of baseline severe impairment of left ventricular ejection fraction (LVEF) on mortality after TAVI.
Methods: Six-hundred-forty-nine patients with aortic stenosis underwent TAVI with the CoreValve system (92.8%) or the Edwards SAPIEN valve system (7.2%). Baseline LVEF was measured by the echocardiographic Simpson method. The impact of LVEF≤30% on mortality was assessed by Cox regression.
Results: Patients with LVEF ≤30% (N=63), as compared to those with LVEF >30% (N=586), had a higher prevalence of NHYA class >2 (p<0.001) and presented with a higher Euroscore (p<0.001). Procedural success was similar in both groups (98.4% vs 97.2%, p=1). After a median follow-up of 436 days, all-cause mortality (23.8% vs 23.7%, p=0.87, HR 0.96, 95% CI 0.56-1.63) and cardiac mortality (19.1% vs 17.6%, p=0.89, HR 1.04, 95% CI 0.57-1.90) were similar in patients with LVEF ≤30% as compared to those with LVEF>30%. Thirty-day all-cause mortality was not significant different between the two groups (11.1% vs 6.3%, p=0.14, HR 1.81, 95% CI 0.81-4.06). Patients with LVEF ≤30%, as compared to those with LVEF >30%, had a trend toward higher risk of 30-day cardiac mortality (11.1% vs 5.3%, p=0.06, HR 2.16, 95% CI 0.95-4.90), which disappeared after multivariable adjustment (p=0.22). In a prespecified subgroup analysis restricted to patients with LVEF≤30%, patients with baseline mean transvalvular gradient <40 mmHg (low-gradient) presented a non-significant higher risk of all-cause death (31.6% vs 12.0%, p=0.14, HR 2.46, 95% CI 0.69-8.74) and of cardiac death (23.7% vs 12.0%, p=0.32, HR 1.90, 95% CI 0.51-7.03) as compared to patients with mean transvalvular gradient ≥40 mmHg (high-gradient).
Conclusions: In this multicenter registry, baseline severe impairment of LVEF was not a predictor of increased short-term and mid-term mortality after TAVI. Among patients with severe impairment of left ventricular function, those with low transvalvular gradient deserve a careful evaluation. Selected patients with severe impairment of left ventricular function should not be denied TAVI.

4988 | BEDSIDE
TAVI in patients with low-flow, low-gradient aortic stenosis and preserved or reduced ejection fraction: results of the German Aortic Valve RegistrY (GARY)

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Objective: Despite severe aortic stenosis (AS; AVA/BSA≤0.6cm^2/m^2) patients (pt) may present a mean transvalvular aortic gradient (MPG) <40mmHg due to LV-dysfunction ("low-flow, low-gradient"; LG-AS) or concentric LV-remodelling with reduced stroke volume ("paradoxical" low-gradient, PLG-AS). The impact of these findings on outcome after TAVI is undetermined. Herein, we analysed the outcome of patients undergoing TAVI for LG-AS (MPG<40mmHg and LVEF<40%), PLG-AS (EF≥50% and MPG<40mmHg) and high-gradient AS (HG-AS: MPG≥40) based on data from the GARY.
Methods and results: 3908pt undergoing TAVI were included in this ongoing non-randomized national multicenter registry. LG-AS, PLG-AS and HG-AS were present in n=359 (9.2%; MPG: 26.5±7.3mmHg; EF: 30.3±7.3%), n=640 (16.4%; MPG: 30.7±6.5mmHg; EF: 60.2±7.8%) and n=1864 (47.7%; MPG: 55.5±13.8mmHg; EF: 56.3±12.5%) pt, respectively. EuroScore I (36.7±20.9 vs. 22.6±15.7 vs. 24.3±17.4; p<0.001) and patient age (79.1±6.1 vs. 80.5±5.6 vs. 81.4±6.1; p<0.001) were significantly different between groups. TAVI was performed transfemorally in the majority (68.5 vs. 68.5 vs. 71.0%, p=n.s.) with a high procedural success rate (>97.1% in all groups).
In-hospital mortality of pt with LG-AS was signficantly higher than with HG-AS (7.8 vs. 4.9%; p=0.029). In contrast, patients with PLG-AS had a comparable in-hospital mortality (P-LGAS 5.3% vs. H-GAS 4.9%; p=0.67). The rate of TAVI-associated complications was without significant differences (new pacemaker: 23.9 vs. 20.0 vs. 22.4%; p=n.s.; cerebrovascular events: 3.3 vs. 3.8 vs. 3.4% p=n.s.). However, postoperative low cardiac output occurred more frequently in patients with L-GAS (8.7 vs. 4.0 vs. 4.2%; p<0.05). Further, patients with L-GAS and P-LGAS required a longer duration of mechanical ventilation compared to H-GAS (30.0±83.6 vs. 37,7±125,0 vs. 24.8±94.1 hours; p=0.015)
Conclusion: Severe aortic stenosis with a mean transvalular gradient <40mmHg is a common finding and present in ≈25% of patients undergoing TAVI. In patients with low-flow, low-gradient AS in-hospital mortality after TAVI is significantly higher, however not in patients with "paradoxical" low gradient AS.

4989 | BENCH
Is early discharge feasible and safe after transfemoral transcatheter aortic valve implantation?

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Background: Length of stay after transcatheter aortic valve implantation (TAVI), as for most medical conditions, is more a product of historical precedent than medical evidence. Shorter hospital stays may be cost-effectiveness and is also supported by the belief that some fraction of the conventional hospitalization may be inefficient, in particular in old and frail patients. We therefore aimed to evaluate the feasibility and the safety of early (i.e., within 3 days) discharge after TAVI.
Methods: Between october 2009 and november 2013, 327 consecutive patients underwent transfemoral TAVI in our institution, all performed using local anesthesia. All the patients were monitored in intensive care unit at least for 24 hours after TAVI. Fourteen (4.1%) patients died before discharge, 8 patients were discharged in an other hospital and were excluded from this study. The remaining 305 patients were discharged at home, 106 (34.8%) within 3 days (early discharge group, EDG) and 199 (65.2%) more than 3 days after TAVI (conventional discharge group, CDG). The primary end point combined death and rehospitalization at 30 days. All adverse events were adjudicated according to the Valve Academic Research Consortium.
Results: Before TAVI, patients in the EDG were less symptomatic, had less renal failure, atrial fibrillation, and previous balloon aortic valvuloplasty than those in the CDG. In contrast, patients in the EDG were more likely to have a pacemaker before TAVI. Patients in the EDG had less frequently major vascular (1.0% vs. 16.4%, p=0.0001) and life-threatening or major bleedings (1.0% vs. 13.7%, p=0.007) complications than those in the CDG. No patient died at 30 days in the EDG, while one patient died in the CDG (p=0.46). The primary end-point occurred in 4 (3.9%) patients in the EDG and in 17 (9.2%) patients in the CDG (p=0.11).
Conclusion: The results of our study suggest that early discharge after TAVI using local anesthesia is feasible and safe in patients with severe aortic stenosis without major complications immediately after TAVI.

4990 | BEDSIDE
Safety and efficacy of local versus general anesthesia in patients undergoing transcatheter aortic valve implantation using a transfemoral approach: VARC-defined outcomes in the FRANCE 2 registry

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Background: Transcatheter aortic valve implantation (TAVI) was first performed under general anesthesia (GA) but evidence is growing that TAVI can be done using local anesthesia (LA) when using the transfemoral approach. We compared VARC-defined outcomes between patients with LA and those with GA for transfemoral TAVI using data from the French national TAVI registry "France 2".
Methods: All consecutive patients underwent transfemoral TAVI between January 2010 and December 2011 in 34 centers were included in the France-2 registry. Outcomes were analyzed by multivariate analysis including all baseline and procedural variables.
Results: A total of 2871 consecutive patients were included; 1002 with LA (34.9%), 1896 (65.1%) with GA. Younger age, female sex, lower STS score, and no peripheral artery disease or porcelain aorta were independent predictors of the choice of LA over GA. The rate of LA increased significantly over time (P<0.001), representing 28% in the 1st registry year vs 41.7% in the 2nd year. The rate of device success and immediate mortality did not differ significantly between LA and GA groups (97.0 vs. 97.6; p=0.12; 3.6 vs. 2.8, p=0.30, respectively). Length of intensive care unit and hospital stay was greater in the GA group vs LA (3.94±6.4 vs. 3.44±4.1 days, p=0.02; 9.8±8.3 vs. 8.8±7.6 days, p<0.001, respectively). Mortality at 30 days and 1 year was similar between groups (8.1% in GA vs 7.6% LA group at 30 days (p=0.44); 17.8% vs. 16.3% at 1 year (p=0.80)). All other VARC-defined outcomes at 30 days and 1 year were similar, including a similar rate of combined safety end-point at 30 days (GA group 39.2 vs. LA group 39.6%, p=0.62) and a similar rate of combined efficacy end-point at 1 year (GA group 34.3 vs. LA group 35.5%, p=0.09).
Conclusion: In this large real-world registry, we observed that transfemoral TAVI performed under LA was as safe and as effective as procedures performed under GA.

4991 | BEDSIDE
Survival and quality of life after surgical aortic valve replacement in octogenarians and high-risk patients

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Purpose: Study the long-term survival, health-related quality of life (HRQOL) and determinants of a change in HRQOL after surgical aortic valve replacement (SAVR) for symptomatic severe aortic stenosis in patients aged >80 or with a logistic EuroSCORE (LES) >20%.
Methods: A prospective single-center cohort study including 1119 consecutive patients operated between 2006 and 2011. Long-term survival was compared to the life expectancy of a matched general population. HRQOL was measured with the SF-36 questionnaire; a physical and mental component scale (PCS and MCS) of 50 equalled the mean of a matched general reference population. We studied the change in PCS between baseline and 1-year follow-up (Cohen's D), and identified variables predictive of this change with multivariable linear regression. Missing data were imputed.
Results: In-hospital and 1-year mortality was 1.8% and 6.9% for octogenarians (n=228), and 6.8% and 16.4% in the LES >20% group (n=73) respectively. During a median follow-up of 2.4 years the survival of octogenarians was similar to patients aged <80 (p logrank = 0.07), and to the life-expectancy in the general population. In the LES >20% group, survival was lower than in patients with a LES <20% (p logrank <0.0001) and below expected for the general population. In octogenarians, the PCS at 1-year follow-up was 49.9, with a moderate increase compared to baseline (Cohen's D 0.62; p<0.001). In the LES >20% group the 1-year PCS was 45.9, with a mild and insignificant increase compared to baseline (Cohen's D 0.40; p=0.06). Female sex, diabetes mellitus, chronic obstructive pulmonary disease, extracardiac atherosclerosis, CCS class and a lower baseline PCS were associated with a lower Cohen's D, age was however not.
Conclusions: In octogenarians both the long-term survival and 1-year HRQOL after SAVR were comparable to a matched general population. Age alone may thus not be a good reason to refrain from sAVR. In patients with a LES >20%, mortality was considerable and the HRQOL remained below expected.

NEW MOLECULAR PLAYERS IN ATHEROSCLEROSIS

5009 | BENCH
Activation of pro-inflammatory T cells by dendritic cells in atherogenesis

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Introduction: Atherosclerosis is a chronic inflammatory disease. Autoantigens

are presented by antigen-presenting cells like dendritic cells (DCs) and lead to the activation of T cells. Recently it has been shown that DCs are able to induce an antigen-specific tolerance in peripheral T cells, which is necessary to suppress the progression of atherosclerosis. In the present study, the cellular composition of atherosclerotic lesions was investigated to analyze the functional role of DCs as activators of pro- or anti-inflammatory T cells.
Material and methods: Cross-sections of 29 plaque specimens were classified as stable (14) and unstable (15) atherosclerotic lesions according to histological criteria (size of the lipid core, thickness of the fibrous cap, neovascularization). Carotid specimens (n=12) without signs of atherosclerosis from accident victims were used as control vessels. Immunohistochemical staining was performed to detect different types of myeloid DCs (S100, fascin, CD83, CD209) and plasmacytoid DCs (CD304, CD123), pro-inflammatory T cells (CD3, CD4, CD8, CD161), and anti-inflammatory Tregs (FoxP3).
Results: In stable compared to unstable lesions, significantly higher numbers of myeloid DCs (S100: 1,6-fold, p=0.01, fascin: 1.6-fold, p=0.03, CD83: 5.2-fold, p=0.003, CD209: 2.5-fold, p=0.004), and pro-inflammatory T cells like T helper cells (3.3-fold, p=0.008), cytotoxic T cells (3.4-fold, p=0.001), and natural killer cells (1.5-fold, p=0.03) were detected. A significant correlation between myeloid DCs and pro-inflammatory T cells (fascin-CD4: r=0.66, $p<0.001$, fascin-CD8: r=0.55, p=0.002, fascin-CD161: r=0.61, $p<0.001$) was visible. For plasmacytoid DCs no correlation was obvious. Also, there was a significantly higher degree of activation of DCs (HLA-DR, 1.6-fold, p=0.03) and T cells (CD25, 6.6-fold, p=0.004) in vulnerable lesions. On the contrary, unstable lesions contained significantly lower numbers of Tregs (0.28-fold, p=0.002). In addition, a significant inverse correlation between myeloid DCs and Tregs could be shown (CD83: r=-0.39, p=0.04, CD209: r=-0.43, p=0.02). Furthermore, plaques of patients treated with statins had a more stable plaque morphology and showed significantly lower numbers of DCs (fascin: 0.47-fold, p=0.006, CD83: 0.28-fold, p=0.04) and significantly higher numbers of Tregs (2.6-fold, p=0.04).
Conclusion: The present data suggest a pro- inflammatory role of myeloid DCs during atherogenesis. The increased inflammatory status in vulnerable plaques seems to result from an imbalance of immune cells with pro- and anti-inflammatory properties such as Tregs.

5010 | BENCH
Downregulation of ITCH prevents atherosclerosis through immune as well as metabolic effects

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Purpose: To assess the role of ITCH, an E3 Ubiquitin Ligase involved in T-cell differentiation in the development of atherosclerosis. We have previously shown that mice lacking ITCH show reduced weight gain and a tendency to M2 (anti-inflammatory) polarization, thus protecting them from the effects of a high fat diet.
Methods: We crossbred ITCH –/– with the hypercholesterolemic mouse model ApoE to generate double knockout mice (ApoE–/–ITCH–/–) and fed the animals a western diet. Histological analysis of the aortic roots was used to compare atherosclerotic burden. RNA expression analyses were used to investigate cholesterol and triglyceride metabolism. FACS analysis characterized the circulating inflammatory cells. To examine the effects of ITCH–/– in the immune compartment alone we performed Bone Marrow Transplant (BMT) experiments.
Results: After 12 weeks of Western Diet (WD) histological analysis of the aortic roots of ApoE–/–ITCH–/–, showed reduced plaque and Oil-red-O staining compared to ApoE–/– animals (90402±9534 μm^2 vs 372382±35540 and 88921±28288 vs. 277590±23305 μm^2 N=8, $p<0.0001$ and $p<0,001$ respectively).
Serum analysis showed a reduction in cholesterol (365,0±80,58 vs 919,2±49,57 mg/dl $p<0,001$ N=5) with no differences in Triglyceride levels.
Liver histology showed ApoE–/–ITCH–/– to be protected from fatty infiltration with a concomitant reduction in the triglyceride content (62,71±3,356 vs 159,4±4,059mg N=4 $p<0,0001$). Gene expression analysis of the liver showed an increase in genes involved lipid metabolism such as PGC1b, STAT6, FABP4 and CPT1a. Furthermore, we found an increase in genes regulating mitochondrial biogenesis and respiration including Nrf1 and Tfam suggesting increased mitochondrial oxidation.
Further to the effects we observed on liver metabolism, ITCH downregulation has been shown to promote a Th2 bias. To dissect the effects of ITCH loss on the immune system from those on the liver we performed BMT experiments. FACS analysis of the KO recipients showed an increase in T-regulatory cells with a concomitant increase in circulating M2 macrophages, while there were no effects on serum cholesterol levels. Aortic root analysis after western diet revealed a much less pronounced decrease in lesion size than in the whole body knockout (145348±2717 vs 189593±20831μm^2 N=3 P=0.1).
Conclusion: Taken together our data suggests that downregulation of ITCH may be beneficial in the setting of atherosclerosis by not only polarizing the immune system towards a less inflammatory phenotype but also affecting lipid metabolism by increasing mitochondrial oxidation.

5011 | BENCH
Effect of myeloperoxidase inhibition on vascular oxidative stress, endothelial function, and atherosclerosis in apolipoprotein E-deficient mice

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Background: Myeloperoxidase (MPO) is an enzyme linked to both inflammation and oxidative stress. In contrast to clinical data, investigation of the impact of MPO on lesion formation in animal models of atherosclerosis has produced controversial results. Aim of the present study was to analyze the of myeloperoxidase inhibition in an animal model of atherosclerosis
Methods and results: 6-8 weeks old apolipoprotein E-deficient (ApoE–/–) mice were fed a high-fat (21% fat) diet containing 1.25% cholesterol for 8 weeks and were concomitantly treated with 4-ABAH (specific MPO-inhibitor) every second day by intraperitoneally administration of two different doses (12.5mg/kg or 25mg/kg body weight) or vehicle. ApoE–/– mice displayed endothelial dysfunction, as indicated by an impaired endothelium-dependent vasodilation (organ chamber), and atherosclerotic lesion formation in the aortic root (oil red O staining; histological morphometric analysis). MPO inhibition in both doses had no significant effects on body weight, cholesterol levels, heart rate and blood pressure. 4-ABAH treatment at lower dosage did not affected oxidative stress (L-012 chemiluminescence), endothelial function and atherosclerotic plaque development, whereas 4-ABAH in higher dosage significantly decreased aortic release of reactive oxygen species (ROS), improved endothelium-dependent vasodilation without influencing endothelium-independent vasorelaxation and reduced significantly atherosclerotic plaque development in the aortic root. Further, to exclude substance specific effects of 4-ABAH in this animal model, we tested NaSCN as a specific inhibitor of MPO. As well, NaSCN reduced significantly atherosclerotic plaque development and oxidative stress with consecutive improvement of endothelial function in hypercholesterolemic ApoE deficient mice. To assess whatever MPO expression in circulating cells influences atherosclerosis, irradiated ApoE–/–-mice were repopulated with bone marrow-derived cells from MPO–/–-mice and were fed a high-cholesterol diet for 8 weeks. MPO deficiency in bone marrow-derived cells resulted in reduced oxidative stress and improved endothelial function with a significant impact on plaque formation. Furthermore, pharmacological inhibition or MPO deficiency in bone marrow-derived cells decreased proinflammatory and increased antiinflammatory cytokines (IL6 and IL10)
Conclusions: Pharmacological inhibition of MPO or MPO deficiency in bone marrow-derived cells leads to inhibition of vascular oxidative stress, endothelial dysfunktion and atherosclerotic lesion formation in ApoE–/–-mice.

5012 | BENCH
Pivotal role of serum- & glucocorticoid-inducible kinase 1 (SGK1) in vascular inflammation and atherogenesis

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Rationale: Atherosclerosis, an inflammatory disease of arterial vessel walls, requires migration and MMP-9-dependent invasion of monocytes/macrophages into the vascular wall. MMP-9 expression is stimulated by transcription factor NF-κB, which is regulated by IκB and thus IκB-kinase IKK. Regulators of NF-κB include SGK1.
Objective: The present study explored involvement of SGK1 in vascular inflammation and atherogenesis.
Methods and results: Gene-targeted ApoE-deficient mice without (apoe–/–sgk1+/+) or with (apoe–/–sgk1–/–) additional SGK1 knockout received a 16-weeks cholesterol-rich diet. According to subsequent immunohistochemistry atherosclerotic lesions in aortic sinus, aortic arch, descending aorta and carotid artery, vascular CD45+ leukocyte infiltration, Mac-3+ macrophage infiltration and MMP-9 positive areas in atherosclerotic tissue were significantly less in apoe–/–sgk1–/– mice than in apoe–/–sgk1+/+ mice. As determined by Boyden chamber and thioglycollate-induced peritonitis, migration of SGK1-deficient CD11b+F4/80+ macrophages was significantly diminished in vitro and in vivo. Zymographic MMP-9 production and invasion through matrigel in vitro were significantly less in sgk1–/– than in sgk1+/+macrophages and in control plasmid- or K127NSGK1-transfected than in S422DSGK1-transfected THP-1 cells. In THP-1 cells MMP-inhibitor GM6001 (25μM) abrogated S422DSGK1-induced MMP-9 production and invasion. According to RT-PCR, MMP-9 transcript levels were significantly reduced in sgk1–/– macrophages and strongly upregulated in S422DSGK1-transfected THP-1 cells compared to control plasmid- or K127NSGK1-transfected THP-1 cells. According to immunoblot analysis IKK- and IκB-phosphorylation was significantly lower in sgk1–/– macrophages than in sgk1+/+macrophages and significantly higher in S422DSGK1-transfected THP-1 cells than in control plasmid- or K127NSGK1-transfected THP-1 cells. Treatment of S422DSGK1-transfected THP-1 cells with IKK-inhibitor BMS-345541 (10μM) abolished S422DSGK1-induced increase of MMP-9 transcription and gelatinase activity. Since MMP-9 release is critical to the arterial remodeling

and plaque destabilization we analyzed neointima formation and plaque rupture in apoe–/–sgk1–/– mice. As a result, we found significantly reduced incidence of plaque ruptures (buried caps) in apoe–/–sgk1–/– mice compared to apoe–/–sgk1+/+ mice.
Conclusions: SGK1 plays a pivotal role in vascular inflammation during atherogenesis. SGK1 controls migration and invasion of monocytes/macrophages as well as MMP-9 production and plaque rupture via regulation of NF-κB.

5013 | BENCH
Protease-activated receptor-2 contributes to atherosclerotic lesion development in apolipoprotein E-deficient mice

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Purpose: The protease-activated receptor-2 (PAR2) is a G-protein-coupled receptor activated by the active coagulation factor X (FXa) or tissue factor/factor VII complex. PAR2 is present on cells of the vessel wall such as vascular smooth muscle cells (SMC) and is up regulated during diabetes and vascular injury. However, the role of PAR2 during the development of atherosclerotic lesions is unclear to date. Thus, we determined the impact of PAR2 for lesions formation in atherosclerosis-prone apolipoprotein E (ApoE)-deficient mice.
Methods: To investigate the effect of PAR2 in atherosclerosis, we generated PAR-2/ApoE double deficient mice. Beginning at an age of 2 months, animals were either fed standard chow or a cholesterol-rich Western diet over 2 or 4 months, respectively, in comparison with ApoE control mice (both C57BL/6 background). Plaques size in the aorta was determined by Oil Red O Staining, FX/FXa, the monocyte marker Mac-2, smooth muscle α-actin and PAR2 by immunostaining. Apoptosis was analysed by Tunel assay. In isolated aortic SMC, IL-6 and MCP-1 were determined by real time PCR.
Results: PAR2 as well as FX/FXa could be found in the lesions of ApoE mice. The size of aortic plaques was significantly reduced in PAR2/ApoE compared to ApoE mice after 2 and 4 moths of Western diet. ApoE mice showed a significant decrease in SMC content within the lesions while apoptosis was markedly increased after 4 months of cholesterol-rich diet in comparison to the PAR2/ApoE. Infiltration of macrophages was significantly higher in ApoE mice and remained elevated at high levels during cholesterol feeding. In comparission, macrophage count was lower in PAR2/ApoE mice in early lesions, however markedly increased during cholesterol feeding. Interestingly, the rate of apoptosis greatly increased in ApoE mice at 4 months, while it remained low in the PAR2/ApoE animals. This may suggest a delayed macrophage infiltration and attenuated apoptosis in the PAR2/ApoE mice. In SMC isolated from C57BL/6 mice the incubation with FXa induced a time-dependent increase in expression of Il-6 and MCP-1. This was attenuated in SMC from PAR2 mice, suggesting a regulatory role of PAR2.
Conclusion: The deficiancy of PAR-2 attenuated the development of atherosclerotic lesions in ApoE mice. Furthermore, we observed decreased apoptosis and delayed macrophage invasion in PAR2/ApoE lesion. A PAR2-dependent regulation of pro-inflammatory mediators such as Il-6 and MCP-1 may contribute to this atherogenic effect of PAR2.

5014 | BENCH
Accelerated coronary atherosclerotic model in a novel low density lipoprotein receptor knock-out swine

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Aims: Acute coronary syndrome is characterized by the rupture of lipid-rich vulnerable atherosclerotic plaque and the mechanism of plaque rupture is still not well established in detail. Several animal models facilitate the evaluation of pathological understanding of atherosclerosis, however no suitable coronary atherosclerotic model using large animal exist. Therefore, we generated low density lipoprotein receptor knockout (LDLR-KO) pigs, which developed coronary atherosclerosis induced by hypercholesterolemia and balloon injury.
Methods and results: LDLR exon regions were deleted in culture porcine fetal fibroblasts. LDLR knockout (LDLR-KO) clone embryos were generated by microinjection of nuclei of fetal fibroblasts into enucleated oocytes. Baseline serum LDL cholesterol level was 510.0±86.1 mg/dL which was extremely higher than of previous reported familial hypercholesterolaemic pig. LDLR-KO pig were fed with 2.0% cholesterol, 20% fat diet and coronary arterial samples (n=54) were obtained 2, 4, 8 and 12 weeks after balloon injury to evaluate the time course of complex lesion development. We found lipid accumulation with foam cells and inflammatory cells from 4 weeks after balloon injury. Macrophage content lesion was evaluated through the use of cathepsin S immunohistochemistry. Time dependent change of the mean ratio of macrophages to plaque area was significantly higher in 4 weeks and 8 weeks model compared with the level at 2 week (8.79±5.98% at 4 week and 17.00±10.38% at 8 week vs 1.14±1.88% at 2 week, P<0.0001, respectively) whereas at 12 week the percentage of cathepsin S area decrease toward the level at 2 week (4.00±4.56%, P=0.66 vs baseline). Developed coronary atherosclerotic lesion containing of lipid pool and necrotic core were observed by 8 week whereas fibrous components were predominantly observed at 12 weeks.
Conclusion: We established a novel accelerated coronary atherosclerotic model in swine using LDLR KO pigs develop early human-like unstable atherosclerotic plaque and can be useful and manageable as a novel coronary atherosclerotic animal model to investigate the mechanism of plaque rupture.

CARDIO-ONCOLOGY: PREVENTING AND MANAGING CARDIOTOXICITY

5069 | BEDSIDE
Right ventricular functions in patients with breast cancer treated with chemotherapy

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Objectives: To assess the effects of chemotherapy on right ventricular (RV) echocardiographic indices
Methods: Echocardiograms (n=200) were performed at baseline and after 4 cycles (101±27 days) of chemotherapy (ChemoRx) in 100 female patients (51±10 years) with breast cancer. The mean cumulative dose of doxorubicin was 234 mg/m^2. RV systolic dysfunction was defined as one of follows: (1) tricuspid annular plane excursion (TAPSE) <16 mm; peak systolic tricuspid annular tissue velocity (S') <10 cm/s; or RV fractional area change <35%. LV systolic dysfunction was defined as a drop of LVEF >10% from baseline and LVEF <55%.
Results: Of 100 patients, 21 and 3 patients developed post-ChemoRx RV and LV systolic dysfunction respectively. RV functions were shown in Table 1. Advanced cancer stage (TNM stage ≥3B) increased risk of RV systolic dysfunction post ChemoRx, Odd ratio=4.62 (1.196-17.881, p=0.02).

Table 1

	Pre-chemotherapy	Post-chemotherapy	P value
Mean arterial blood pressure (mmHg)	92±9	91±9	0.35
RV systolic function			
RV fractional area change (%)*	56±9	50±11	<0.01
Tricuspid annular plane excursion [TAPSE] (mm)*	22±3	20±3	<0.01
Tricuspid peak systolic annular tissue [lateral S'] (cm/s)*	13±2	12±2	<0.01
RV diastolic function			
Tricuspid early annular tissue velocity [e'] (cm/s)*	10.9±2.8	10.0±2.3	<0.01
Tricuspid E/e'*	5.7±1.9	6.0±1.5	0.04
Tricuspid E/A*	1.4±0.4	1.3±0.3	<0.01
Tricuspid E deceleration time (msec)	252±77	243±72	0.32
Hepatic venous diastolic reversal velocities (cm/s)	27±9	28±8	0.37
Right atrial volume index (ml/m^2)	18±5	19±6	0.15
Global RV function – RV Tei index*	0.28±0.18	0.36±0.17	<0.01
LVEF (%)*	70±7	67±7	<0.01
RV systolic pressure (mmHg)	27.4±4.7	27.1±4.0	0.64

Conclusions: (1) RV systolic, diastolic, and global functions were significantly impaired after ChemoRx. (2) RV systolic dysfunction post ChemoRx was more prevalent than LV systolic dysfunction. (3) Further studies regarding prognosis of RV dysfunction in these patients are needed.

5070 | BENCH
Subchronic, but not acute daunorubicin cardiomyopathy is associated with a downregulation of stem cell markers, stem cell factor and vascular endothelial growth factor in the heart

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Purpose: Our aim was to determine the expression of stem cells markers in rat heart of acute and subchronic model of daunorubicin (DAU)-induced cardiomyopathy, and the expression of growth factors, cytokine stem cell factor (SCF) and its receptor c-kit, which could participate in regeneration of injured heart.
Methods: Acute cardiomyopathy was induced in male Wistar rats (10-12 weeks old) by i.p. administration of DAU (6 injections every 48h, 3 mg/kg). Single i.v. injection of DAU (15 mg/kg) was used to induce subchronic cardiomyopathy. Controls received vehicle. Hemodynamic parameters were measured by left ventricular catheterization. After 2 weeks (acute cardiomyopathy) and 8 weeks (subchronic cardiomyopathy), animals were sacrificed. Expressions of ANP, VEGF, HGF, IGF-1, SCF, markers of cardiac progenitor (c-kit, Mdr1), endothelial progenitor (CD34, CD133, c-kit) and mesenchymal (CD44, CD105, c-kit) stem cells at mRNA level were determined by qRT-PCR in samples of left ventricles.
Results: As expected, daunorubicin administration led to a decreased body and absolute heart weight, decreased function of left ventricle (decreased LVP, dP/dtmax, dP/dtmin) and it caused 30% mortality in the subchronic model. Expressions of ANP increased in the left ventricle in both models. In acute model of cardiomyopathy, we found downregulated expression of CD34 and an upregulated expression of CD105. There was no change in expression of other markers, SCF and growth factors. In the subchronic model, the expression of SCF, c-kit

and markers of endothelial and mesenchymal stem cells were significantly decreased. We observed a decreased expression of VEGF, but no change for HGF and IGF-1. Mdr1 expression was increased in both models.
Conclusion: Downregulation of SCF in subchronic DAU-induced cardiomyopathy could lead to reduced chemotaxis and migration of stem cells from the bone marrow. Decreased c-kit expression could also reflect the apoptosis of cardiac progenitor cells and reduced mesenchymal and endothelial stem cell markers could reflect impaired stem cell homing in this setting. Downregulation of VEGF might contribute to impaired mobilization of stem cells, but it could also be associated with defective angiogenesis. Surprisingly, the model of acute cardiomyopathy had likely a lesser impact on mobilization, homing and survival of stem cells. Pharmacological modulation of mobilization and homing of stem cells could be a potentially effective strategy in treatment of subchronic daunorubicin-induced cardiomyopathy.
Grant support: VEGA 1/0981/12, APVV-0887-11

5071 | BEDSIDE
Myocardial deformation imaging detects early left ventricular dysfunction in patients submitted to chemotherapy with anthracyclines

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Introduction: Cardiotoxicity can be a secondary effect of chemotherapy (CT) with anthracyclines and other drugs, such as monoclonal antibodies anti-Her2. Monitoring of left ventricular function is therefore crucial. A higher reproducibility and sensitivity of myocardial deformation imaging, compared to the conventional assessment of left ventricular function, was demonstrated in other contexts of cardiac disease.
Objective: To evaluate the usefulness of myocardial deformation imaging for early detection of cardiotoxicity, in patients submitted to CT with anthracyclines.
Methods: Prospective study of 34 patients (50.4±12.5 years-old), 74% females, referred for CT with anthracyclines (doxorubicine n=15, epirubicine n=19). Echocardiographic evaluation was done one week before the beginning of CT (T0), one week after the first cycle (T1), one week after the third cycle (T2) and one week after the conclusion of CT (T3). In each moment, conventional echocardiographic evaluation of the left and right ventricular dimensions and systolic and diastolic function was performed, as well as 2D-speckle tracking strain evaluation of the left ventricle.
Results: A significant reduction of global longitudinal strain (GLS) was observed throughout the CT: T0 (-22.0±2.6%), T1 (-20.0±2.9%), T2 (-19.5±2.4%) and T3 (-17.3±1.9%), $p<0.0005$. Global circumferential strain (GCS) also showed a significant decrease: T0 (-28.3±3.9%), T1 (-24.7±4.1%), T2 (-23.6±4.1%) and T3 (-21.9±4.5%); $p<0.0005$. Left ventricular ejection fraction (LVEF) also decreased (66.6±4.0% at T0; 63.9±3.2% at T1; 62.3±2.8% at T2; 60.0±3.5% at T3; $p<0.0005$). At T3, GLS was > -19% in 26 patients (76%) and > - 15% in 2 patients (6%). All patients had a LVEF ≥55% at T3 and 5 (15%) had a reduction ≥10%. A GLS at T2 > -17.5% had a sensitivity of 80% and a specificity of 83% to predict a ≥10% LVEF drop between T0 and T3. There were no significant differences for tissue Doppler or for diastolic or systolic function parameters of the right ventricle. There were no correlations between the cumulative dose or anthracycline type and the echocardiographic findings.
Conclusions: There was a significant decrease of GLS and GCS immediately after the first cycle of CT, suggesting a very early cardiotoxic effect. At T3, around 3/4 of the patients had a GLS value considered a long-term predictor of heart failure. In contrast, LVEF diminished but within normal values and only 15% of the patients had a decrease ≥10%. Myocardial deformation imaging should be part of the echocardiographic monitoring of these patients.

5072 | BEDSIDE
Cardiac toxicity related to nimotuzumab administration in oncologic population

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Purpose: Monoclonal antibodies cardiac toxicity has been deeply studied since they are widely used in oncology. Nimotuzumab, a novel monoclonal antibody has been used in head and neck neoplasms, glioma, and recently cervical cancer. No reports have been published yet regarding nimotuzumab cardiotoxicity. Traditionally assessment of left ventricular ejection fraction (LVEF) in oncologic patients has been done with radionuclide ventriculography. The aim of this study is to find whether there is any relationship between LVEF reduction and nimotuzumab using cardiac magnetic resonance (CMR) since it is a better method in terms of accuracy and is free of radiation.
Methods: We analyzed an established cohort of mexican women. 30 patients were included, with ages in the range of 30-65 years old with diagnosis of cervical cancer stage IV-B and no previous cardiovascular history. We performed CMR, one week before nimotuzumab administration. Patients received 3 sessions of nimotuzumab during 18 months follow-up. After that time we performed another CMR. We applied a t test for paired groups, a value of $p<0.05$ was considered statistically significant.
Results: There is a statistically significant reduction in LVEF after 18 months follow-up when compared with basal measurements (61.5%±8.3% vs 56.6%±8.3%, p=0.03) Two patients developed late-enhancement in septal area.
Conclusions: It is demonstrated in our cohort a LVEF reduction that can be explained by nimotuzumab. Nevertheless more studies need to be conducted in order to increase the study population. On the other hand, two patients developed late-enhancement which could indicate fibrosis induction. This is the first report showing an important relationship between nimotuzumab and cardiac function. It is also relevant because we implement a non-traditional method for LVEF screening in oncologic patients.

5073 | BEDSIDE
Cardiac sympathetic nerve activity of I-123 MIBG imaging is unrelated to left ventricular dysfunction during trastuzumab therapy

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Purpose: Trastuzumab is a humanized monoclonal antibody that binds to the extracellular domain of the human epidermal growth factor receptor 2 (HER2) and inhibits breast cancer proliferation. Cardiotoxicity has been reported to occur with trastuzumab when administered alone and in combination with antineoplastic agents, particularly anthracyclines. Cardiac iodine-123 metaiodobenzylguanidine (I-123 MIBG) imaging is useful to estimate cardiac sympathetic nerve activity. Many studies indicate that assessment of impaired I-123 MIBG uptake would be useful for the evaluation of anthracycline cytotoxicity. However, it remains unclear the relationship between trastuzumab-induced cardiotoxicity and cardiac sympathetic nerve damage using I-123 MIBG imaging. The aim of this study was to assess the value of I-123 MIBG scintigraphy in breast cancer patients treated with trastuzumab who showed a decrease in their cardiac function.
Methods: We performed cardiac I-123 MIBG imaging in 19 female breast cancer patients (mean age 52±12 years, range 31-70 years) who demonstrated a significant cardiotoxicity during trastuzumab therapy. Cardiotoxicity was defined as a left ventricular ejection fraction (LVEF) decrease below 60% measured by echocardiography. I-123 MIBG imaging was obtained at the early (15 min after tracer injection) and delayed (4 hr after) phases. The heart to mediastinum ratio (H/M) and the global washout rate (WR) were calculated.
Results: 2 patients (11%) were treated with trastuzumab alone and 17 patients (89%) were used in combination with anthracyclin-based regimens. 11 patients (58%) had radiotherapy, of whom 6 patients on the left breast. The mean of delayed H/M ratio was 2.92±0.73 (1.77-4.48) and the mean of WR was 20.6±7.7% (8.2-35.8). I-123-MIBG scintigraphy showed abnormal H/M ratio (<2.0) in one patient and slightly increased WR (>30%) in three patients. LVEF was no correlation with the delayed H/M ratio (r=-0.20, p=NS) and WR (r=-0.12, p=NS), respectively.
Conclusions: These data indicate that trastuzumab-induced LV dysfunction do not reflect cardiac adrenergic neurone abnormalities. The mechanism of trastuzumab-induced cardiotoxicity may differ from anthracycline -induced cardiac neurotoxicity.

NOVEL ANTICOAGULANTS: TRIALS, COST, REAL LIFE USE

5108 | BEDSIDE
Efficacy and safety of apixaban vs edoxaban for stroke prevention in non-valvular atrial fibrillation: an indirect treatment analysis

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Purpose: Vitamin K antagonists (VKA) have been standard of care for the prevention of stroke in patients with non-valvular atrial fibrillation (NVAF). However, the novel oral anticoagulants (NOACs) apixaban, dabigatran and rivaroxaban offer a therapeutic advantage over standard VKA treatment. Results for an additional NOAC, edoxaban have recently been published and the aim of this analysis was to compare the efficacy and safety of apixaban and edoxaban in the management of NVAF.
Methods: Data from two phase III, double-blind randomised controlled trials were included: apixaban [ARISTOTLE, apixaban 5 mg bid (n=9,120) vs warfarin (n=9,081]; edoxaban [ENGAGE AF-TIMI, 30 mg od (n=7,034) vs 60 mg od (n=7,035) vs warfarin (n=7,036)]. An adjusted indirect comparison using Bucher methodology and a network meta-analysis (NMA) were performed, using warfarin as the common control.
Results: Apixaban was significantly more efficacious than edoxaban 30 mg for the prevention of both stroke or systemic embolism and ischemic stroke. Apixaban had an intermediate safety profile between the two edoxaban doses, with a significantly lower incidence of major or clinically relevant non-major bleeding (CRNM) vs edoxaban 60 mg, compared with a higher incidence vs edoxaban 30

Table 1. Results of indirect comparison

Outcome	Odds ratio (95% CI)	
	Apixaban vs edoxaban 30 mg	Apixaban vs edoxaban 60 mg
Stroke or SE	0.69 (0.55, 0.88)*	0.91 (0.71, 1.16)
Ischaemic stroke	0.67 (0.50, 0.88)*	0.95 (0.71, 1.27)
Major or CRNM bleeding	1.14 (0.99, 1.30)	0.81 (0.71, 0.93)*
Major bleeding	1.49 (1.21, 1.84)*	0.88 (0.73, 1.08)
Intracranial haemorrhage	1.37 (0.85, 2.22)	0.92 (0.59, 1.44)
All-cause mortality	1.03 (0.88, 1.20)	0.98 (0.84, 1.14)
Total discontinuations	0.96 (0.87, 1.06)	0.90 (0.81, 0.99)*

CI, confidence interval; CRNM, clinically relevant non-major bleeding; SE, systemic embolism. *$p<0.05$.

mg. Compared with apixaban, patients treated with edoxaban 60 mg were more likely to discontinue treatment (Table 1).
Conclusions: Based on this indirect comparison analysis, apixaban offered a significant benefit over edoxaban 30 mg for stroke prevention. When compared with edoxaban 60 mg, apixaban was superior for the reduction of major or CRNM bleeding and had lower discontinuations.

5109 | BEDSIDE
Potential impact of apixaban on formulary budget and clinical outcomes in non-valvular atrial fibrillation patients

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Purpose: The goal of this study was to assess impact of apixaban on resource utilization in patients with non-valvular atrial fibrillation (NVAF) to the NHS in the United Kingdom.
Methods: A model was developed to analyze the impact of introducing apixaban in a representative NVAF population on 5-year total healthcare costs. Treatment patterns and market share projections were based on current market research data, with assumptions of projected future market shares. Model assumes that the apixaban market share is drawn equally from dabigatran, rivaroxaban, vitamin K antagonist (VKA) and aspirin. Effect size of apixaban versus VKA and aspirin were derived from randomized controlled trials and against other novel oral anticoagulants from indirect treatment comparisons. Measured in 2012 values, cost inputs were obtained from the published data sources. Annual discounting rate of 3.5% was applied.
Results: Model projected that 384,400 patients (62% of the treatment eligible population) would be treated with anticoagulants over the 5-year study period. Assuming a 10% uptake of apixaban over 5 years, an increase of 1.2% (~£25.6 million) in the total healthcare budget was estimated including medical cost savings of ~£11.1 million. This translated into net increase of £13.33 per treated patient per year from the NHS perspective. More importantly, 322 strokes, 417 major bleeds, 515 CRNM bleeds, 94 myocardial infarctions and 406 CV hospitalizations were avoided during the 5-year study period with the addition of apixaban (Fig. 1).

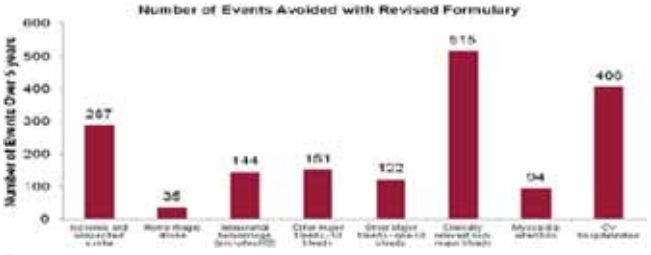

Figure 1

Conclusions: Addition of apixaban has a minimal increase in the healthcare budget over a 5-year period. This addition provides better outcomes with drug costs offset by medical cost savings elsewhere.

5110 | BEDSIDE
Cost-effectiveness of high-dose edoxaban compared to adjusted-dose warfarin for prevention of stroke and systemic embolism in non-valvular atrial fibrillation

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Purpose: High-dose edoxaban has been shown to be non-inferior to adjusted-dose warfarin for the prevention of stroke or systemic embolism in non-valvular atrial fibrillation (NVAF) patients; while resulting in lower rates of intracranial hemorrhage (ICH) and cardiovascular death. We assessed the cost-effectiveness of high-dose edoxaban compared to adjusted-dose warfarin for the prevention of stroke and systemic embolism in patients with NVAF.
Methods: A Markov model was constructed to compare the cost-effectiveness of high-dose edoxaban (60 mg once daily, 30 mg daily in patients with a creatinine clearance of 30-50 mL/minute, a body weight of ≤60 kg or the concomitant use of a potent P-glycoprotein inhibitor) and adjusted-dose warfarin (target international normalized ratio (INR) range of 2.0-3.0) from a United States (US) payer/Medicare perspective. The base-case analysis assumed a cohort of 70-year-old patients with NVAF at moderate-to-high risk of ischemic stroke (CHADS2≥2), a creatinine clearance >30 mL/minute and no previous contraindications to anticoagulation. Data sources included the Edoxaban versus Warfarin in Patients with Atrial Fibrillation Trial (ENGAGE AF-TIMI 48) and other studies of anticoagulation. Outcome measures included life-time costs in 2013 US dollars, quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs).
Results: In the base-case analysis, patients treated with high-dose edoxaban lived an average of 10.32 QALYs at a lifetime treatment cost of $100,223. Those receiving adjusted-dose warfarin lived an average of 10.12 QALYs and incurred costs of $111,719; suggesting high-dose edoxaban to be a dominant economic strategy. These results were most sensitive to changes in associated costs and utility of edoxaban and warfarin (including INR testing, clinic visits and patient time), the monthly cost of treating ICH and the model's time horizon. Upon Monte Carlo simulation, high-dose edoxaban was found to be cost-effective in 76% of the 10,000 iterations, assuming a willingness-to-pay threshold of $50,000/QALY.
Conclusion: Our Markov model suggests high-dose edoxaban is a cost-effective alternative to adjusted-dose warfarin for the prevention of stroke and systemic embolism in NVAF patients at an increased risk of stroke.

5111 | BEDSIDE
Uptake in new oral anticoagulation agents in anticoagulant naive atrial fibrillation patients: nationwide data 2011-2013

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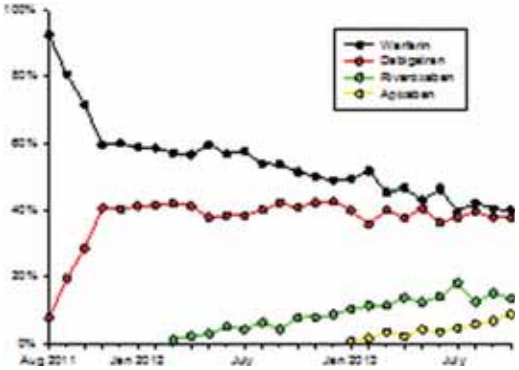
Purpose: New oral anticoagulation (OAC) agents have been approved for stroke prophylaxis in atrial fibrillation (AF). In "real-world" registries we investigated how these new drugs are being adopted.
Methods: Using a Danish nationwide administrative dataset we identified all OAC-naïve AF patients initiating OAC from August 22nd, 2011 through October 31st, 2013. Baseline characteristics and temporal utilization trends were compared between initiators of warfarin vs. one of the new OACs: dabigatran, rivaroxaban, or apixaban.
Results: We included 18,611 OAC-naïve AF patients; 9902 (53%) initiated warfarin treatment, 7128 (38%) dabigatran, 1303 (7%) rivaroxaban, and 278 (1%) apixaban. Uptake of dabigatran was quick, and 40% of newly initiated patients were started on dabigatran within the first 4 months of when the drug came on market (Figure). By October, 2013 40% were being started on warfarin and dabigatran, respectively, and another 20% were started on either rivaroxaban or apixaban. Rivaroxaban and apixaban users generally had a higher predicted risk of stroke and bleeding, i.e. higher CHA2DS2-VASc and HAS-BLED scores, compared to warfarin and dabigatran users. Older age, female gender, and a prior stroke were some of the factors associated with new OAC use vs. warfarin, whereas chronic kidney disease, myocardial infarction, and heart failure showed the opposite association.



Uptake in new OAC agents among OAC-naive.

Conclusions: In a contemporary setting among OAC-naïve patients with AF who are initiated on an OAC; the use of warfarin has declined since the introduction of dabigatran in August 2011. This shift in treatment patterns could result in major winnings for patients with AF. Compared to warfarin, new OACs are more frequently used in older and female patients.

5112 | BEDSIDE

Real world discontinuation among early users of apixaban, dabigatran, rivaroxaban or warfarin among atrial fibrillation patients newly initiated on anticoagulation therapy: tell of first 200 days

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Purpose: This study evaluated discontinuation of apixaban, dabigatran, and rivaroxaban in the first 200 days after launch in patients with atrial fibrillation (AF) in the US real-world clinical practice setting.
Methods: A retrospective cohort study was conducted using MarketScan® including the Earlyview data. AF Patients >18 years (ICD-9 code 427.31 or 472.32) with one year of baseline period were included if they were newly prescribed the novel oral anticoagulants (NOACs) during the first 200 days after their availability in the US market, or newly prescribed warfarin after apixaban launch. Discontinuation was defined as lack of subsequent prescription of the index drug within 30 days after the last supply day of the last prescription. Cox proportional hazards model was used to compute hazard ratio (HR) of discontinuation, adjusting for potential confounders and other important patient characteristics.
Results: Among 17,356 eligible patients, 841 (4.85%) were initiated with apixaban, 5,805 (33.45%) with dabigatran, 2,125 (12.24%) with rivaroxaban and 8,585 (49.46%) with warfarin. The mean age of apixaban, dabigatran, rivaroxaban and warfarin patients were 70.3±12.0 years, 69.1±12.4 years, 69.2±12.1 years and 71.9±12.3 respectively. After adjusting baseline patient characteristics, apixaban was significantly less likely to discontinue versus rivaroxaban (HR: 0.60; CI: 0.48, 0.74) and warfarin (HR: 0.55, CI: 0.45 - 0.67) (Figure).

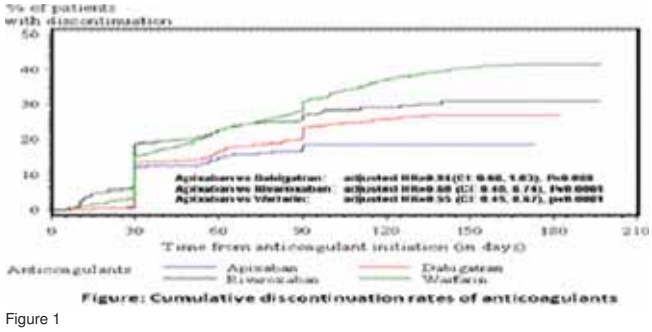

Figure 1

Conclusion: The risk of discontinuation was lower for apixaban versus rivaroxaban or warfarin among newly anticoagulated AF patients. These early findings with relatively short follow-up should be confirmed in future with larger sample size and longer term follow-up.

Poster Session 6

RESPONSES TO EXERCISE TESTING AND TRAINING

P5114 | BEDSIDE

Impact of low versus upper range intensity exercise training on metabolic markers of endothelial function and oxidative stress in patients with coronary artery disease

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Purpose: To evaluate the impact of low versus upper range intensity exercise training on endothelial function, through assessment of circulating blood markers of endothelial function: the stable end product of nitric oxide (NOx), dimethylarginine (ADMA), symmetric dimethylarginine (SDMA), xanthine oxidase (XO), and advanced oxidative protein products (AOPPs, marker of oxidative stress) in patients (pts) with stable coronary artery disease (CAD).
Methods: Fifty one male pts admitted at residential rehabilitation center were studied. Patients were randomized to low intensity exercise (65% of maximal heart rate; LI group, n=26; mean age 56.9±7.8 years) and to upper range intensity exercise (85% maximal heart rate; UI group, n=25; 53.1±8.0 years). Patients exercised twice a day at residential center over a period of 3 weeks. At baseline and 3 weeks later, in all pts values of NOx, ADMA, SDMA, XO and AOPPs were evaluated and exercise test was performed.
Results: After 3 weeks NOx increased significantly in both groups: in LI group (from 36.7±10.1 to 42.0±14.2 μmol/l, P=0.021), and in UI group (from 33.4±7.3 to 44.6±9.9 μmol/l, P<0.0005). Value of ADMA as well of SDMA decreased significantly in both groups after 3 weeks: in LI (P<0.005 and P=0.004) and in UI group (P<0.005 and P<0.005).
Compared to the baseline, value of XO at the end of the study was significantly lower in both groups (P<0.0005 both), however at the end of the study value of XO was significantly lower in UI than in LI group (P=0.023). AOPPs also decreased in both groups: in LI (from 311.7±17.8 to 301.9±20.7 μmol/L, P=0.027) and in UI group (from 307.2±16.6 to 274.9±59.2 μmol/L, P=0.011), and at the end of the study was significantly lower in UI than in LI group (P=0.048).
After 3 weeks level and duration of test increased in both groups, nevertheless level and duration of exercise test was significantly higher only in UI group, compared to baseline exercise test (P=0.012 and P<0.005).
Conclusions: Residential 3 weeks low, as well as, upper range intensity exercise training induced improvement in metabolic markers of endothelial function and oxidative stress in patients with CAD. More significant increase of NOx, decrease of SDMA, AOPPs and increase of exercise capacity in UI group give an advantage to upper range over low intensity exercise training in patients with CAD.

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Cardiopulmonary exercise testing in patients with left bundle branch block: A new method to detect or exclude ischemic heart disease

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Between 2007 and 2012 we performed 5,781 cardiopulmonary exercise stress tests (CPET) at our Institute's CPET core laboratory. Aim of the study was to determine the outcome of patients with left bundle branch block (LBBB) with diagnosis of ischemic heart disease (IHD). Ischemic heart disease was present in 59% of patients, chronic heart failure (CHF) in 22%, valvular heart disease (VHD) in 13% and hypertension in 6%. Myocardial ischemia (MI) was detected in 21 patients with IHD (pos), and excluded in 338 (neg) on the basis of previously-described criteria. Briefly, MI was considered when double slope sign in DVO2/DWR slope combined with a negative downward flattening in O2pulse are both evident (AUC 0.84), while MI was excluded when the above abnormalities were not present. All CPET studies were stopped for exhaustion (92%) or dyspnea (8%) at a RER>1.05.
In 21 IHD-pos the most significant difference with IHD-neg was in DVO2/DWR slope (7.8 (1.5) vs 8.9 (1.8), P<0.001), and O2pulse at peak exercise (9.2 (2.6) vs 12.4 (2.3) ml/b, P<0.001). Follow up lasted 36 (11) months. Patients with IHD-pos had 12 cardiovascular events (CABG in 6; PCI in 4, ACS in 2), while IHD-neg had only 2 events (PCI in 2, P<0.001). In conclusion, CPET – a inexpensive, non-operator dependent, safe and noninvasive test- may be used in patients with LBBB to detect/exclude myocardial ischemia on the basis of VO2kinetics and O2pulse.

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Value of high-frequency QRS analysis compared to conventional ST-segment analysis in patients with chest pain and normal ECG

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Background: The novel analysis of high-frequency QRS components (HFQRS-analysis) has been proposed in patients with chest pain (CP) and non-diagnostic baseline screening for coronary artery disease referred for exercise tolerance test (ex-ECG) with ST-segment-analysis.
Objective: To compare the diagnostic value of ex-ECG to ex-HFQRS-analysis in the emergency setting.
Methods: Chest pain (CP) patients with baseline nondiagnostic ECG, troponin, and echocardiography were considered. Exclusion criterion was QRS duration ≥120 msec. All patients underwent ex-ECG for conventional ST-segment-analysis and ex-HFQRS-analysis. The HFQRS intensity was calculated and a decrease ≥50% of the signal recorded in two contiguous leads, at least, was considered as an index of ischaemia, as ST-segment depression ≥2 mm or ≥1 mm when associated with CP at ex-ECG.
Endpoint: The composite of coronary stenosis ≥50% or acute coronary syndrome, revascularization, cardiovascular death at 3-month follow-up.
Results: Out of 175 patients considered, 142 were enrolled (age 58±17 years). Maximal exercise heart rate was 145±19 bpm and systolic blood pressure 171±23 mmHg. Fifteen patients achieved the endpoint. Receiver operator characteristics (ROC) analysis showed the incremental diagnostic value of HFQRS intensity during stress over the conventional ex-ECG with ST-segment analysis (area under ROC curve of ex-ECG versus ex-HFQRS as follows: 0.596 versus 0.682; 95% Confidence Intervals 0.43-0.77 versus 0.54-0.82; p=0.225 and p=0.022, respectively; C statistic p=0.223). The ex-HFQRS-analysis showed higher sensitivity (73% vs. 20%; p<0.01), lower specificity (63% vs. 99%; p<0.001), and comparable negative predictive value (95% vs 91%; p=NS) when compared to ex-ECG-analysis.
Conclusions: In patients with CP the novel ex-HFQRS-analysis shows a valuable incremental diagnostic value over the ex-ECG with ST-segment-analysis.

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Patients with primary microvascular angina present functional capacity impairment comparable to systolic heart failure patients

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Purpose: The primary microvascular angina (PMA) is a chronic condition associated to the impairment of the quality of life and an increase risk of cardiovascular events. Despite this evidence, there is scarce information about the functional capacity and chronotropic response in patients with PMA. We aimed at assessing the functional capacity and cardiopulmonary test variables obtained in patients with PMA, patients with systolic heart failure (HF) and healthy controls.
Methods: We studied 15 patients with PMA, defined as presence of typical angina associated with reversible perfusion defects in myocardial perfusion scintigraphy and no obstructive epicardial coronary lesions on coronary angiography (6 men, 54.4±8.9 years and BMI = 31.1±5.5 kg/m^2); 14 HF patients (10 men, 55.8±13.2 years, NYHA class II – III and BMI = 29.7±4.5 kg/m^2) and 15 healthy controls (8 men, 48.6±11.6 years and BMI = 28.1±5.3 kg/m^2). The 3 groups underwent maximal cardiopulmonary exercise testing (RER ≥1.1) using a treadmill protocol.
Results: No significant difference was found between groups regarding age and BMI ($p>0.05$). PMA patients presented higher values for left ventricular ejection fraction (65.8±11.7%) when compared to HF patients (33.4±17.6%), $p<0.0001$. PMA and HF groups showed similar peak VO2 (19.7±5.4 and 17.6±3.2 ml/kg/min, $p>0.05$), but both values were reduced as compared to control group (27±5.6 ml/kg/min), $p<0.0001$. VO2 at anaerobic threshold also presented comparable values between PMA (11.8±2.6 ml/kg/min) and HF patients (11.4±2.1 ml/kg/min), $p>0.05$; being both values reduced as compared to controls (15.7±3.2 ml/kg/min), $p<0.0001$. The chronotropic reserve in PMA (60.2±20.1 bpm) and HF patients (49.4±23.9 bpm) were also similar ($p>0.05$), but reduced as compared to control group (87.3±15.1 bpm), $p<0.0001$.
Conclusion: Our results indicate that patients with PMA present a significant reduction in functional capacity and impaired chronotropic reserve similar to that exhibited by patients with systolic HF. The mechanisms responsible for these changes demand further investigation.

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Impact of cardiovascular risk factors and pre-test symptoms on relationship between age and peak heart rate during treadmill testing in women

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Background: We sought to determine the effects of cardiovascular risk factors (CVRFs) and pre-test symptoms on the intercept and slope of the linear relationship between peak heart rate (pHR) and age during exercise treadmill testing (ETT).
Methods: Consecutive women who underwent symptom-limited Bruce protocol ETT at our clinic from 1994 - 2010 were included. Women with cardiovascular disease or on beta blockers were excluded. The relationship of pHR to age, pre-test symptoms, and CVRFs was evaluated with linear regression in 2 models: first, age only included; second, age, pre-test symptoms, current smoking, diabetes, obesity, hypertension, and hyperlipidemia added to the model. $P<0.01$ was considered significant.
Results: 11,029 women (90% Caucasian, age 52±12 years, Duke Treadmill Score 4.9±4) were included. Baseline pre-test symptoms were reported in 3632 women (32.9%). CVRFs included: smoking 8.4%, diabetes 3.5%, obesity 26.4%, hypertension 15.8%, hyperlipidemia 16.9%. Peak HR was predicted as 201 - 0.67 x age ($r=0.495$, $p<0.0001$). Table shows the effect of CVRFs on pHR. Smoking has the greatest effect (-6.8 bpm), followed by obesity, diabetes, and pre-test symptoms. Though significant, effects of hypertension and hyperlipidemia were small. The slope of pHR versus age was not appreciably affected by addition of CVRFs or pre-test symptoms.

The effect of CVRFs and pre-test symptom

	Intercept	Parameter Estimate	p-value
Peak heart rate vs age relationship			
Age	201	–0.67	<0.0001
CV risk factors and symptoms status effect on peak heart rate vs age relationship			
	204		
Age		–0.68	<0.0001
Current Smoking		–6.75	<0.0001
Obesity		–3.60	<0.0001
Diabetes		–3.02	<0.0001
Symptom status		–2.59	<0.0001
Hypertension		–1.19	0.001
Hyperlipidemia		–1.01	0.0036

Conclusions: CVRFs and pre-test symptoms lower pHR achieved during ETT in women but do not appreciably change the relationship of pHR versus age.

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Associations of exercise capacity and heart rate recovery with carotid-femoral pulse wave velocity

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Purpose: Arterial stiffness and exercise variables such as exercise capacity (EC) and heart rate recovery (HRR) are known cardiovascular risk predictors. The purpose of this study is to investigate the associations between treadmill test variables with arterial stiffness.
Methods: Study population consisted of 139 subjects, 81 men and 58 women, age 40-65 years old, free of cardiovascular disease history that underwent treadmill test which showed no evidence of ischemia. EC was assessed through peak metabolic equivalents (METs) and HRR was measured at 2 min post exercise. Arterial stiffness was evaluated through carotid-femoral pulse wave velocity (CF-PWV).
Results: Pearson's correlation revealed that CFPWV is associated with HRR ($r=-0.262$, $p=0.003$) and Spearman's correlation with EC ($rho=-0.183$, $p=0.036$). Linear regression analysis revealed that both HRR and peak METs are predictors of arterial stiffness (table).

Linear regression analysis that shows the associatons of HRR and EC with CFPWV after adjusting for common confounders

	r2	Beta	Sig.
Model HRR:	0.232	–0.212	0.012
HRR, Gender, Age Smoking, b-blockers, Hypertension			
Model EC:	0.236	–0.238	0.008
Peak METs, Gender, Age, Smoking, b-blockers, Hypertension			

CFPWV was also associated with age, male gender and smoking.
Conclusions: The associations between arterial stiffness and slow HRR/reduced EC in apparently healthy individuals could be partially explained by impaired baroreflex sensitivity and endothelial dysfunction. Further experimental research is required to illuminate the underlying mechanisms.

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Chronotropic incompetence detected on screening exercise treadmill testing is a strong predictor of long-term mortality even when present in individuals on a beta blocker or calcium channel antagonist

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Purpose: To test the hypothesis that chronotropic incompetence (CI) is predictive of mortality in individuals screened for cardiovascular disease
Methods: 34,551 consecutive exercise treadmill tests (TMET) in individuals without previously documented heart disease, but including treated hypertensives were analyzed using impaired heart rate reserve as a marker for CI.
Results: 5327 (15.4%) had CI - 67.9% were male.There were 1275 deaths over a median follow-up of 12.4 years. The mortality in individuals with CI was over twice that for non CI patients - 6.89% versus 3.11% ($P<0.0001$).
Multivariate analysis demonstrated that chronotropic incompetence was a strong predictor of long-term mortality in this large cohort of individuals undergoing screening TMET, with a hazard ratio of 1.99 [95% confidence interval 1.76 to 2.25, $P<0.0001$].
CI retained its predictive power for long-term mortality both in the presence and absence of heart rate modifying medications. CI was a more powerful predictor of late mortality than a positive exercise ECG response, which had a hazard ratio of 1.31 [1.10 to 1.57, $P=0.0027$].
Female sex was protective for better late survival, with a hazard ratio of 0.64 [0.56 to 0.73, $P<0.001$], while treatment with a negatively chronotropic drug was a weak negative predictor of late mortality (likely a consequence of associated hypertension) with a hazard ratio of 1.22 [1.06 to 1.40, $P=0.005$].

Long-term mortality by sex and chronotropic incompetence (TMET measured HR reserve <80% of predicted HR reserve) in the presence and absence of heart rate modifying drugs

	Chronotropic incompetence	Normal HR reserve	P value
No HR modifying drugs			
Male	7.02%	3.05%	<0.0001
Female	4.48%	2.39%	<0.0001
With HR modifying drugs			
Male	12.42%	6.49%	<0.0001
Female	5.48%	2.65%	=0.0085

Conclusions: Chronotropic incompetence during TMET is a strong predictor of long-term mortality, even in the presence of heart rate modifying drugs. Chronotropic incompetence overall had a stronger predictive power for long-term mortality than a positive exercise ECG response in this study.

P5121 | BEDSIDE

Effect of bosentan on cardiopulmonary exercise testing in patients with pulmonary arterial hypertension or inoperative chronic thromboembolic pulmonary hypertension

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Purpose: Cardiopumonary exercise testing (CPX) was reported to be useful for patients with pulmonary arterial hypertension (PAH). However, few reports exist in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH). We investigated whether an oral endotheline receptor antagonist (ERA), bosentan, affected parameters of CPX in CTEPH similar to those in PAH.
Methods: We examined PAH and CTEPH patients who visited our hospital from September 2009 to June 2013. Patients who had a clinical diagnosis of PAH or inoperable CTEPH base on the Dana Point criteria and whose World Health Organization functional class (WHO-FC) were from II to IV were included. Bosentan was administered to 17 PAH and 12 CTEPH. Bosentan was given at a dose of 62.5 mg twice daily for 4 weeks, followed by 125 mg twice daily, thereafter. All patients underwent CPX, which was performed before bosentan therapy and at 3 to 6 months of the treatment.
Results: The mean age of the patients was 47±17 (16-80) years old. There were 8 (28%) men and the mean disease duration was 1.7 years. Bosentan was well tolerated by all patients, and there was no evidence of drug-related liver dysfunction. No accidents were reported during CPX in either of the groups. In PAH patients, peak VO_2 significantly increased after bosentan treatment (p=0.009). On the other hand, in CTEPH patients, there were no significant differences in the peak VO_2. However, the peak $PETCO_2$ was significantly increased from 23.9±5.2 mmHg at baseline to 29.3±10.7 mmHg after the bosentan treatment (p=0.040). Peak heart rate during exercise and plasma BNP levels tended to decrease after the bosentan therapy in both PAH and CTEPH (p=0.089 and p=0.067, respectively). Interestingly, the change from baseline in peak VO_2 was correlated with pulmonary vascular resistance in PAH (r=0.489, p=0.046). However, in CTEPH, they were not correlated (r=0.060, p=0.85).
Conclusions: Bosentan therapy partially improved the exercise capacity in patients with inoperable CTEPH demonstrated by an improvement of the peak $PETCO_2$. Bosentan therapy improved the exercise capacity, indicated by the peak VO_2 and VE/VCO_2 slope in patients with PAH. CPX is quite helpful for assessing exercise capacity of patients with inoperable CTEPH as well as PAH under the treatment with an ERA.

P5122 | BEDSIDE

Pulse pressure reserve during treadmill ECG to stratify risk of long-term mortality and myocardial infarction

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Purpose: Exercise electrocardiography (eECG) is widely used for risk-prediction in suspect coronary artery disease (CAD), although its predictive accuracy, based on standard interpretive criteria, is deemed suboptimal. We tested standard and newer variables as predictors of combined all-cause mortality and myocardial infarction (MI)
Methods: We screened all patients with suspect CAD and a clinically-indicated eECG during year 2007. Patients with known CAD, uninterpretable electrocardiogram or severe valvular disease were excluded. The remaining 636 patients comprised the study cohort for this retrospective analysis (mean follow-up 6.1 years) of total mortality or MI. Duke treadmill score (DTS)<–5 was considered abnormal. Pulse pressure (PP), systolic minus diastolic blood pressure, was computed at rest and peak exercise. Reserve-PP was defined as PP at peak exercise minus PP at rest.
Results: Results are shown in the table. Hard events were 67. The best cutoff for reserve-PP to predict hard events was <30, although the only variables which finally remained significant at multivariate analysis were: age (>64), male gender and ischemic ST depression.

Predictors of hard events

Cox analysis	Univariable		Multivariable	
Patient characteristics	Hazard ratio	P-value	Hazard ratio	P-value
Age>64 y/o	6.9 (3.8–12.7)	<0.0001	7.1 (3.9–13.1)	<0.0001
Male	2.1 (1.2–3.7)	0.01	2.4 (1.4–4.3)	0.0001
Diabetes	2.6 (1.5–4.8)	0.005	–	ns
ST tract depression	2.9 (1.4–6)	0.005	2.1 (1–4.4)	<0.05
METS<10	1.82 (1.1–3)	<0.01	–	ns
1 min HRR<15	2.4 (1.4–4)	0.001	–	ns
Reserve-PP<30	1.8 (1.1–2.9)	0.03	–	ns

Table shows that reserve-PP <30 does not remain a significantly negative prognostic marker of mortality and myocardial infarction, after correction for other simple prognosticators, Duke treadmill score <–5 was not significant also at univariate analysis (not shown).

Conclusions: This is the first study testing the value of reduced reserve-PP specifically during eECG. We demonstrate it confers worse prognosis regarding hard events, but not increasingly to simple demographic variables and ST depression.

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Age and fitness level are strongest limitations of exercise capacity during inpatient cardiac rehabilitation

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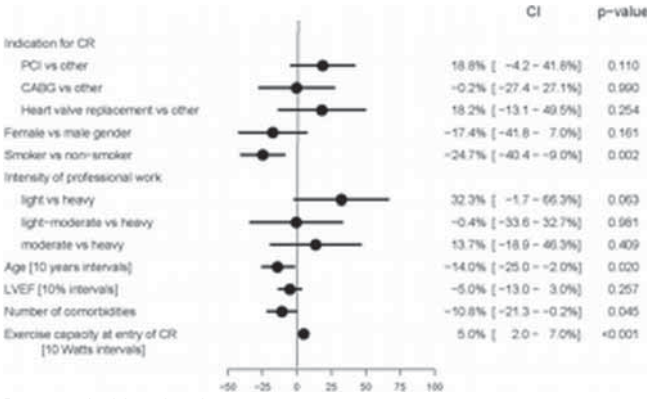
Purpose: Exercise training is a core component of Cardiac Rehabilitation (CR). We aimed to identify factors associated with increase of training volume (TV) and fitness during CR.
Methods: We analyzed sociodemographic and clinical data from a prospective registry of 557 patients (mean age 51.7±6.9 years, 87.9% men), who were referred to inpatient CR after PCI (62.5%), CABG (16.2%) and heart valve replacement (9.5%). At admission, a bicycle stress test was performed to determine exercise intensity. TV as a product of exercise intensity (Watt) and time (min) was collected at admission and end of CR. Cardiopulmonary exercise testing (CPX) was performed at discharge for defining fitness according to VO2peak.
Results: Training frequency was 11.3±2.7/3 weeks and intensity 90.7±9.7% of maximum heart rate (81% continuous, 19% interval training). Increase of TV of 784.3±623.4 Watts x min was significantly associated with smoking, blue or white collar work and exercise capacity at entry of CR (figure). Fitness at the end of CR was significantly influenced by age (7.7% of variance), increase of TV during CR (4.2%), exercise capacity at entry (3.6%), indication for CR (2.1%) and gender (1.0%).



Parameter of training volume increase

Conclusion: Patients were trained with high intensity and most of them reached a considerable increase of their TV. Because fitness at the end of CR was influenced by age, exercise capacity at admission and increase of TV during CR, especially patients from the age of 50 should continue training in after care programs to preserve work ability.

P5124 | BEDSIDE

Effect of 3 weeks of aerobic exercise training on neuropsychological status of patients undergoing coronary artery bypass grafting

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Purpose: To evaluate the effect of three weeks of aerobic exercise training on neuropsychological status in patients with coronary artery disease (CAD) after on-pump coronary artery bypass grafting (CABG).
Methods: 92 male patients with CAD, who have undergone on-pump CABG, were examined and assigned into 2 groups: group 1 with cycling training program (n=39, the mean age – 55.5±5.33 years) and group 2 without cycling training program (n=53, the mean age 57.2±6.21 years). Cycling training began on postoperative day 14 and continued for 3 weeks. The patients in both groups were comparable by clinical and demographic data as well as by neuropsychological and intraoperative parameters. Neuropsychological status was assessed using the automated software complex “Status PF” on days 5-7 before CABG and 1 month after it. The following parameters were assessed: complex visual-motor reaction time, functional mobility of nervous processes and brain performance (reaction time and missed target signals) attention (Burdon’s attention test), memory (10 numbers memorizing test). The statistical analysis was conducted using Statistica 6.0.
Results: No focal neurological symptoms were seen 1 month after CABG in both groups. Faster complex visual-motor reaction time was observed in patients with cycling training (500.7±55.1 ms vs. 535.1±64.1 ms, p=0.03) as well as lower rate of missed target signals during the functional mobility of nervous processes test (10.1±1.2 vs. 14.0±1.3, p=0.04), a great number of processed signs on minute 1 (102.1±27.7 vs. 77.7±33.5, p=0.01) and minute 3 (118.1±28.4 vs. 101.2±25.5, p=0.03) and attention coefficient (60.9±20.9 vs. 48.4±19.9, p=0.03) while com-

pleting the Burdon's attention test compared to the patients without cycling training. No significant differences in memory performance were seen in both groups.
Conclusions: Three weeks of aerobic exercise training improves neuropsychological status in patients undergoing CABG.

P5125 | BEDSIDE
Necessary dosage adjustments in post myocardial infarction pharmacotherapy to optimize exercise performance during cardiac rehablitation programs

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Purpose: Classical post myocardial infarction pharmacotherapy may need dosage adjustments when serious modifications in health habits are taken, as it happens in participants in cardiac rehabilitation programs (CRP), who generally improve quickly their blood pressure, lipid and glycaemic profiles, leading to reductions in doses of ACEIs/ARAII, statins, and anti-diabetics respectively.
Methods: We analysed our data from the cardiac rehabilitation unit, including 108 patients who completed the program in 2013. We assessed all modifications in drug doses necessary to optimize the pharmacotherapy to fit best progressive improvements in pressure, lipid and glycaemic parameters during the three-month CRP.
Results: Mean systolic and diastolic blood pressure decreased 26,02 mmHg and 12,4 mmHg respectively from the beginning to the end of the program, (systolic 95% CI 19-32 mmHg; $p<0.01$ and diastolic 95% CI 7-15 mmHg; $p<0.05$), which supposed that 78 participants (72,22%) needed readjustments to half doses of ACEIs in the final weeks of the CRP, remaining normotensive and with better tolerance to exercise after dose readjustment. Furthermore, lipid profile in the last blood test, that is to say 12 week after the beginning of the CRP, revealed that 64 patients (59,25%) had less than 50 mg/dl of LDL cholesterol, and therefore, reduction to half doses of statins was also applicable to them. 7 participants who were taking Ezetimibe and 12 with Fenofibrate were prescribed to stop these treatments thanks to normalization of lipid profiles, despite continuation with statins was recommendable to all of them. 34 non-insulin-dependent diabetic patients, who began the program with Metformin 850 mg, 3 times a day evidenced a better glycaemic profile, reducing Metfomin to 500 mg b.i.d. in the last two weeks of the training program, when verification of a mean decrease of HbA1c of 1,23 mg/dl (95% CI 0.96-1,54 mg/dl) was done.
Conclusions: Cardiac rehabilitation modifies intensively health habits, involving mainly improvement in lipid, blood pressure and glycaemic profiles. Therefore, treatment adjustments during the program become necessary to optimize their physical performance, without forgetting the remarkable pharmacological savings and the better quality of life that treatment reductions suppose.

CARDIOVASCULAR HEALTH UP IN SMOKE

P5127 | BEDSIDE
Fifteen year follow-up of patients with premature (<36 years) myocardial infarction: the impact of smoking status on recurrent coronary events

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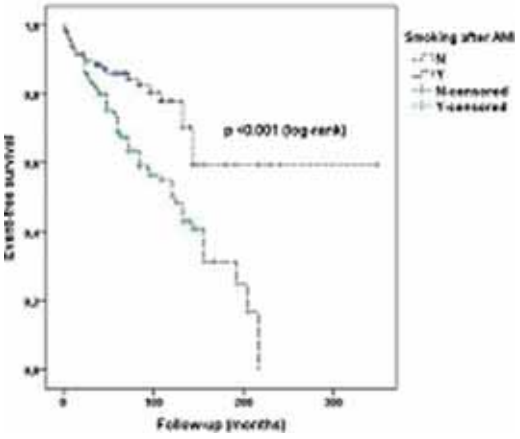
Purpose: There are few data regarding the long-term prognosis in very young survivors of myocardial infarction (MI). The present study sought to explore the long-term outcome in individuals who had sustained a MI at the age of ≤35 years.
Methods: We recruited 261 consecutive patients who had survived their first MI ≤35 years of age. Patients were followed-up for up to 15 years. Clinical end points were: readmission for acute coronary syndrome, cardiac death or coronary revascularization due to clinical deterioration.



Unadjusted Kaplan-Meier survival curves.

Results: The most prevalent risk factor at presentation was smoking (93.6%). Follow-up data were obtained from 236 patients (32.2±3.7 years old, 203 men). The median period of follow-up was 8.8 years (inerquartile range: 5-13 years). During follow-up 138 (58.5%) patients reported continuation of smoking. Eighty-nine (37.7%) patients presented cardiac events (12 deaths, 58 acute coronary syndromes, 19 revascularizations). Multivariable Cox regression analysis showed that persistence of smoking was an independent predictor of cardiac events after adjustment for conventional risk factors (sex, age, diabetes mellitus, hypertension, hypercholesterolemia, family history of coronary artery disease) [hazard ratio (HR): 2.43; 95% confidence interval (CI): 1.49 to 4.02; p=0.001]. Continuation of smoking remained an independent predictor for recurrence of cardiac events when additional adjustment for ejection fraction at presentation was performed (HR: 2.24; CI: 1.34 to 3.75; p=0.002). The figure shows the unadjusted Kaplan-Meier survival curves for cardiac events according the continuation of smoking after MI.
Conclusions: Persistence of smoking is a predictor of poor long-term prognosis in patients with premature MI.

P5128 | SPOTLIGHT
Time-dependent relation between smoking cessation and improved exercise tolerance in apparently healthy middle-age men and women

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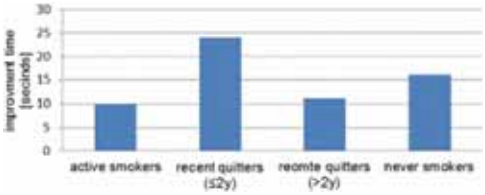
Background: Smoking is an independent cardiovascular risk factor and correlates with reduced exercise tolerance. Data on the time dependent effect of smoking cessation on exercise tolerance are limited.
Methods: We investigated 17,115 men and women who were annually screened at the Institute for Medical Screening of the Chaim Sheba Medical Center. All subjects had their smoking status documented and performed an exercise stress testing (EST) according to Bruce protocol at each visit. Subjects were divided at baseline into four groups: active smokers (N=2,858), recent quitters (smoking cessation ≤2 years before baseline EST; N=861), remote quitters (smoking cessation >2 years before the baseline EST; N=3,856) and never smokers (N=9,810). Baseline and follow up EST duration were compared among the four groups.
Results: Recent quitters demonstrated a 2.4-fold improvement in their EST duration compared to active smokers (improvement of 24±157 vs. 10±157 seconds, respectively; p=0.02; figure). Multivariate logistic regression showed that recent quitters were 26% more likely to improve their exercise tolerance compared with active smokers (95% CI [1.08-1.47], p=0.003). Assessing smoking status as a time-dependent covariate during 4 consecutive visits demonstrated that recent quitters were 17% more likely to improve their exercise tolerance compared to active smokers (CI 1.02-1.34, p=0.02), with a less pronounced benefit among remote quitters (HR=1.11, CI 1.02-1.21, p=0.01).



Improvement according to smoking status.

Conclusions: Smoking cessation is independently associated with improved exercise tolerance. The benefits of smoking cessation are evident within the first 2 years of abstinence.

P5129 | BEDSIDE
Characteristics of persistent smokers and quitters after an acute coronary syndrome

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Purpose: To identify the characteristics of persistent smokers after ACS, compared to patients who quit smoking.
Methods: We analysed data from RESPONSE, a multicenter RCT. Patients (18-80 years) were included within 8 weeks after an acute coronary syndrome (ACS). As part of the main study patients were randomised to a nurse-coordinated prevention program in addition to usual care (intervention) or usual care alone. For this analysis, we omitted the group assignment. Quitters are defined as smoker at time of hospitalization and stopped in the one year follow-up. Persistent smokers kept smoking until one year follow-up.
Results: Information on smoking behaviour was available in 709 (96%) patients. 186 (57%) patients had a quit attempt in the year after the event, of which 128 (69%) immediately after the event. The majority of successful quitters stopped after the event and 156 (48%) remained quitted until one year follow up. 168 (51%) patients were persistent smokers despite the ACS event. Persistent smok-

ers more often had a positive history in CVD compared to quitters (26% vs. 13%), more often a BMI>25 (32% vs. 24%) and less often a higher education profile (15% vs. 33%).

Characteristics of quitters vs. smokers

Baseline characteristics	Quitters[1] (n=156)	Smokers (n=168)
Positive history of CVD, n (%)	19 (13%)	44 (26%)
Risk profile at baseline		
Hypertension (>140 mmHg syst)	36 (24%)	33 (20%)
LDL >2.5 mmol/L	46 (31%)	66 (39%)
Overweight (BMI >25)	35 (24%)	53 (32%)
Education rates, n (%)		
Fewer than 8 years	41 (28%)	63 (38%)
College or university	49 (33%)	25 (15%)
Risk profile at 12 months follow-up		
Hypertension (>140 mmHg syst)	41 (28%)	43 (26%)
LDL >2.5 mmol/L	32 (22%)	62 (37%)
Overweight (BMI >25)	127 (81%)	112 (67%)

Conclusion: The majority of quitters stopped immediately after their ACS event and were more successful than subsequent quitters. To improve strategies for smoking cessation we should focus on relapse prevention for these late stoppers.

P5130 | BEDSIDE
Risk factor profile of patients with myocardial infarction: smoking in younger patients

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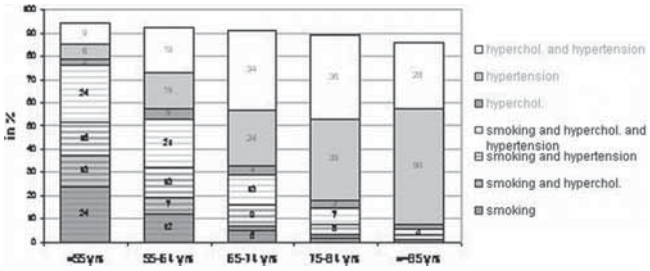
Background: Besides age and sex, smoking, hypercholesterolemia, and hypertension are the main risk factors that promote the development of coronary artery disease and are included in prognostic scores for calculating coronary risk (ESC European guidelines on cardiovascular disease prevention). We have therefore analysed whether risk factor profiles for patients with myocardial infarction (MI) differ between ages and whether younger patients show these 3 risk factors more often

Methods: The Berlin Myocardial Infarction Registry collects data on hospital treatment of MI patients prospectivcely since 1999. Part of data collection is asking patients anamnestically for their risk factors. We examined 5 age groups with n=6009 with <55 yrs., n=6342 with 55-64 yrs., n=8214 with 65-74 yrs., n=6174 with 75-84 yrs. and n=2523 with ≥85 yrs.

Results: The risk factor profile differed across ages, 76% of those <55 years were smokers and 94% of those <55 years had at least one of the three risk factors (fig.). Over time the risk factor profile in the age group <55 years remained almost the same: 1999-00: 76% smoked, 2001-02: 73%, 2003-04: 77%, 2005-06: 75%, 2007-2008: 77%, 2009-10: 74%, 2011-12: 76%. In the younger age group there was only a small difference between sexes, with 76% of men and 74% of women smoking.



Risk factor profile according to age.

Conclusions: Patients suffering from MI in the younger age group <55years were smokers in 76%. In our data, smoking became the most important risk factor for developing MI in younger years. Since 1999 the percentage of smokers in the younger age group <55years has not decreased.

P5131 | BEDSIDE
Tobacco smoke exposure is associated with alterations of cardiac geometry and function in children

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Background: Passive smoking (PS) is associated with increased risk for cardiovascular events, however, there has been little information on cardiac function in children with PS. The purpose of this study is to assess left ventricular (LV) function in PS children.

Methods: Echocardiography with tissue Doppler imaging was performed in 93 children (age:10±3 years) who have been exposed to tobacco smoking since intrauterine life and 124 age-matched children without PS. Left atrial anteroposterior diameter, LV end-diastolic volume, ejection fraction, LV mass, and mass-to-volume ratio were measured. Transmitral peak flow velocities during early (E) and late diastole (A) and mitral annular myocardial velocities during early (Em) and late diastole (Am) were measured. Left atrial systolic force was calculated. Isovolumic relaxation time and tissue Doppler-derived myocardial performance index were assessed. Effective arterial elastance was estimated by end-systolic pressure/stroke volume index. End-systolic elastance was calculated by a modified single-beat method.

Quantitative B-mode ultrasound scans were used to measure intima-media thickness (IMT) and diameters of the common carotid artery.

Results: Body mass index and heart rate were similar between the 2 groups ($p>0.05$). Systolic and diastolic blood pressures were significantly higher in PS children than in controls (112±10 vs. 109±9 and 63±8 vs 60±8 mmHg, $p<0.05$, respectively). Compared with controls, left atrial size, LV mass, mass-to-volume ratio, and left atrial systolic force were significantly higher (2.6±0.40 vs. 2.4±0.31 cm, 90±46 vs. 79±31 g, 1.07±0.22 vs. 1.01±0.02, and 3.86±2.05 vs. 3.24±1.69 kdyne, $p<0.05$, respectively) and Em/Am ratio was significantly lower (2.97±0.67 vs. 3.16±0.77, $p<0.05$) in PS children. Ejection fraction,isovolumic relaxation time, myocardial performance index, effective arterial elastance,end-systolic elastance, and intima-media thickness did not differ between the 2 groups.

Conclusions: The present study indicates that tabacco smoke exposure can adversely affect LV geometry and function in childhood. Passive smoking may contribute to the increased prevalence of later cardiovascular diseases.

P5132 | BEDSIDE
Adolescent smoking and vascular function in the SAPALDIA youth study

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Background: Early exposure to tobacco smoke is associated with various adverse health outcomes in children and adolescents. However, little is known on the impact of active smoking on cardiovascular health (CVH) in adolescence. The SAPALDIA Youth Study, a nested study in the Swiss Study on Air Pollution and Lung and Heart Disease In Adults (SAPALDIA) cohort, investigated the association between active smoking and functional vascular properties.

Methods: In 288 SAPALDIA offspring underwent a clinical examination following a standardized protocol: blood pressure (BP), ultrasound assessment of the CCA, anthropometry, blood draw for cardiovascular biomarkers and serum cotinine. Offspring and parents gave information on early life, health and lifestyle of the child, including smoking status. We conducted multivariable regression analyses on the impact of active smoking on vascular compliance ($p \times ((2\times$ delta Lumen Diameter $\times$ diastolic Lumen Diameter) + (delta Lumen Diameter)2)/(4 $\times$ Pulse Pressure)) and pulse pressure (PP: mean systolic – mean diastolic BP), adjusting for main confounders and parental smoking in 271 offspring (mean age 15 yrs., 53% girls)

Results: Weekly smoking was reported by 10% and current parental smoking by 24%. Mean (SD) of compliance was 1.40 mm^2/kPa (0.29), systolic BP 114 mmHg (12.9), diastolic BP 65 mmHg (8.5) and of PP 49mmHg (10.6) Regression analyses yielded significant effect estimates for weekly smoking (compliance -0.164 mm^2/kPa, 95%CI -0.295; -0.033, and PP: 6.8 mmHg, 95%CI 1.7; 11.8). Serum cotinine (by 10 μg/l) analyses supported our findings (compliance: -0.03 mm^2/kPa, 95%CI -0.076; 0.005; PP: 0.18 mmHg, 95%CI 0.02;0.3). Results remained consistent after adjusting for parental smoking.

Conclusion: The analyses yield evidence of an early adverse impact of active tobacco exposure on vasculature in adolescence, independent of parental smoking. This short-term impact is suggestive of potential long-term cardiovascular health consequences of early smoking and underlines the need for early prevention of uptake of cigarette smoking in youth.

P5133 | BEDSIDE
Impact of smoking habit on coronary plaque vulnerability as assessed by integrated backscatter intravascular ultrasound

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Background: Although smoking habit is a well-established risk factor for coronary artery disease (CAD), little is known about the relationship between smoking habit and coronary plaque vulnerability.

Objectives: We assessed the association between smoking habit and the coronary plaque vulnerability of nonculprit lesions as assessed by integrated backscatter intravascular ultrasound (IB-IVUS).

Methods: Eighty-four consecutive patients with stable CAD who received statin treatment and underwent percutaneous coronary intervention were enrolled. Nonculprit coronary lesions with mild to moderate stenosis were measured by IB-

IVUS. IB-IVUS images were recorded at an interval of 0.5 mm for 10 mm length in each plaque. Patients were divided into two groups: a smoking group and a non-smoking group.
Results: There were no significant differences in plaque volume (PV) and percentage of PV (%PV, 100×PV/Vessel Volume) between the two groups. Lipid volume (LV) and percentage of LV (%LV, 100×LV/PV) in the smoking group were significantly higher than those in the non-smoking group (27.7±14.9mm^3 vs. 21.1±9.9mm^3, P=0.023 and 42.7±12.8% vs. 36.2±11.6%, P=0.019, respectively). Furthermore, multiple regression analysis with other metabolic variables revealed that smoking habit was independently associated with %LV (p=0.036) among IVUS parameters.
Conclusions: Nonculprit coronary lesions in patients with smoking habit were associated with more lipid-rich plaque content, indicated that the patients with smoking habit may increase vulnerable plaque and the risk of CAD events.

P5134 | BEDSIDE
Relation of airflow limitation and smoking status to carotid atherosclerosis in patients with coronary artery disease

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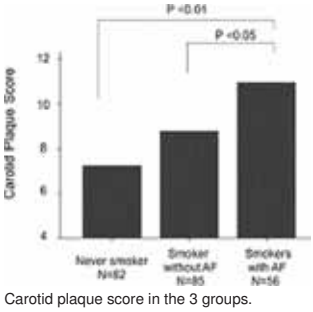
Purpose: Chronic obstructive pulmonary disease (COPD) is associated with an increased risk of morbidity and mortality from cardiovascular disease. However the effects of smoking seem to be insufficient to explain all of cardiovascular risk in COPD. The aim of this study was to evaluate the combined effects of smoking and airflow limitation (AF) on severity of carotid atherosclerosis among patients with coronary artery disease (CAD).
Methods: A total of 223 patients with stable CAD were classified into the smokers with AF group (n=56), the smokers without AF group (n=85), and the never smokers group (n=82). All subjects underwent spirometry and carotid ultrasonography. Current or past smokers were classified as smokers. AF was defined as ratio of forced expiratory volume in one second to forced vital capacity <0.70. Carotid plaque score (PS) was calculated by summing all plaque thicknesses in both of the carotid systems. Severe carotid atherosclerosis was defined as the carotid PS >10.
Results: The prevalence of severe carotid atherosclerosis was significantly higher in the smokers with AF group (53.6%) than in the smokers without AF group (35.3%) (p=0.038) and the never smokers group (25.6%) (p=0.001).
On multivariate logistic regression analysis, the smokers with AF group was an independent predictor of severe carotid atherosclerosis (odds ratio, 3.16; 95% confidence interval, 1.35-7.38; p=0.008). Associations were consistent in subgroups, including smoking status, the duration of smoking, and the amount of cigarettes smoked per day.



Carotid plaque score in the 3 groups.

Conclusions: In patients with CAD, the smokers with AF were more likely to have carotid atherosclerosis than in those without. Our findings might explain the increased risk of future cardiovascular events in such patients.

P5135 | BEDSIDE
Effect of smoking cessation on HDL function

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Background: Smoking cessation reduces cardiovascular disease (CVD) and improves health outcomes. Although the oxidative modification of HDL by smoking could reduce the functionality of HDL, the impact of smoking cessation on HDL function has not been studied.
Purpose: We studied the effect of smoking cessation on HDL function.
Methods: Thirty-two smokers were randomly treated with varenicline or nicotine patch for 24 weeks. The plasma lipid profile, malondialdehyde level, and the cholesterol efflux capacity and anti-oxidative capacity of HDL were measured before and after treatment.
Results: The rate of smoking cessation was 78.6%. There was a significant correlation between efflux capacity and body mass index (BMI) (r= -0.44, p=0.01). After the study period, BMI and plasma uric acid were significantly increased (p<0.001, p<0.05, respectively) and plasma malondialdehyde, pulse rate, hemoglobin, systolic blood pressure and the carbon monoxide (CO) level were significantly decreased in the successful smoking cessation group (p<0.05, p<0.05, p<0.001, p<0.05, p<0.001, respectively). The change in the cholesterol efflux capacity was inversely associated with the reduction of CO (r= -0.45, p=0.02). Although there was no difference in HDL subfractions as analyzed by capillary isotachophoresis between the successful and unsuccessful smoking cessation groups, there were significant differences in the anti-oxidative and cholesterol efflux capacity of HDL between the groups.
Conclusion: These results indicate that cigarette smoking reduces HDL function and smoking cessation leads to the improvement of HDL functionality, which may be one mechanism by which smoking cessation has beneficial effects against CVD.

P5136 | BEDSIDE
Twelve weeks of successful smoking cessation therapy with varenicline increases serum apolipoprotein a-I and high-density lipoprotein cholesterol levels

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Purpose: Cigarette smoking adversely affects lipid profiles, and smoking cessation should improve lipid profiles in the long term. However, it remains unclear whether intensive, medication-based smoking cessation therapy can affect lipid profiles in the short term. Thus, we evaluated the short-term effects of smoking cessation therapy with varenicline on lipid profiles.
Methods: Participants included 90 consecutive subjects who received 12 weeks of smoking cessation therapy. All subjects were treated with varenicline, and no changes were made to their current lipotropic and antidiabetic medications during treatment. At first and last visits, lipid profiles and fasting blood glucose and hemoglobin A1c levels were evaluated and physical examination was performed. The success group, comprising subjects who attained exhaled carbon monoxide–confirmed 4-week continuous abstinence, included 73 subjects, whereas the failure group, comprising those who did not achieve complete smoking cessation, included 17 subjects. The number of cigarettes consumed per day was reduced in all subjects in the failure group.
Results: Serum apolipoprotein A-I (apoA-I) and high-density lipoprotein cholesterol (HDL-C) levels significantly increased from baseline to 12 weeks in the success group (apoA-I: 150.1±28.3 vs. 157.6±27.5 mg/dL, respectively, p<0.01; HDL-C: 53.9±15.7 vs. 57.4±14.4 mg/dL, respectively, p<0.01); however, there were no statistically significant differences observed in the failure group (apoA-I, 145.9±33.4 vs. 146.8±34.2 mg/dL, respectively, p=0.87; HDL-C, 52.6±15.7 vs. 53.3±16.3 mg/dL, respectively, p=0.80). The effect sizes (Cohen's d) of apoA-I and HDL-C in the success group were 0.56 and 0.47, respectively. The post-hoc statistical power of apoA-I and HDL-C in the success group were 0.97 and 0.98, respectively.
Conclusion: These findings suggest that successful smoking cessation therapy with varenicline improves serum apoA-I and HDL-C levels in the short term.

P5137 | BEDSIDE
Vascular functional and morphological alterations in smokers with varenicline therapy

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Purpose: Varenicline has been reported to achieve high rates of smoking cessation. It remains undetermined whether varenicline therapy improves vascular function in smokers. We sought to examine whether smoking cessation with varenicline therapy has beneficial effects on vascular function in smokers.
Methods: Seventy two smokers (57±12 years) succeeded in complete smoking cessation and were consecutively enrolled into this study. Vascular function was assessed by brachial arterial flow-mediated dilatation (FMD), nitroglycerin-induced vasodilatation and brachial intima-media thickness (baIMT) before and 20 weeks after administration of varenicline. FMD and baIMT were measured simultaneously using a semi-automatic vessel wall tracking software program. Suprasystolic compression at least 50 mmHg above systolic blood pressure was performed at the forearm for 5 minutes and longitudinal images of the brachial artery were continuously recorded from 0 second after cuff inflation to 5 minutes after cuff release for the FMD measurement. 75 μg dose of a nitroglycerin tablet were sublingually administered and longitudinal images of the brachial artery were continuously recorded from 0 second to 8 minutes after nitroglycerin administration for the nitroglycerin-induced vasodilatation measurement.
Results: All 72 subjects succeeded in complete smoking cessation and exhaled carbon monoxide decreased significantly (20.0±11.1 ppm, before vs. 1.9±1.5 ppm, after 20 weeks, p<0.001). FMD was significantly improved after 20 weeks (4.09±1.83%, before vs. 4.77±2.33%, after 20 weeks, p=0.010), whereas nitroglycerin-induced vasodilatation and baIMT were not significantly changed. Multivariate regression analysis showed improvement of FMD correlated independently with FMD (r=-2.668, p=0.010) before administration of varenicline.

Conclusion: Smoking cessation with varenicline therapy significantly increased FMD without significant changes of nitroglycerin-induced vasodilatation and baIMT from before to 20 weeks. It appears to improve vascular function which depends on endothelial function, not on vascular smooth muscle function or changes in vascular structure in smokers.

P5138 | BEDSIDE
Comparison of two strategies for smoking cessation in hospitalized patients

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Background: Hospitalization is considered a window of opportunity for smoking cessation. There is little data in the literature about smoking treatment for hospitalized patients. Smoking is a major risk factor for cardiovascular global risk.
Objectives: To compare the effectiveness of two smoking cessation strategies based on cognitive behavioural therapy initiated in hospitalized patients and to evaluate the factors related to relapse.
Methods: A prospective randomized study with 90 smokers hospitalized in the University Hospital Antonio Pedro (HUAP), Niterói, Brazil, from January to December 2012 was carried out. The degree of nicotine dependence was assessed by the Fagerstrom test and the degree of craving by the Questionnaire of Smoking Urges-Brief (QSU-B). Patients were divided into 2 treatment groups: BI (Brief Intervention, n=45) and II (Intensive Intervention with the presentation of an educational video produced by the authors, n=45). All patients were assessed by telephone in the first, third and sixth month after discharge to assess relapse. Abstinence was confirmed by carbon monoxide measurement in exhaled air (COex). Of the 90 patients, 61.1% were male; average age 51.1±12.2yo.
Results: The main causes for hospitalization were cancer (23.3%), cardiovascular diseases (21.1%) and respiratory diseases (14.4%). The degree of nicotine dependence was elevated in 43.4% and withdrawal symptoms were present in 58.9%. The average COex initial approach was 4.8±4.5ppm, correlated positively with the Fagerstrom score (r=0.244, p=0.02) and negatively with days without smoking (r=0.284, p=0.006). After 6 months follow-up, 40.7% patients continued abstinent (BI=9 & II=24) and 59.3% had relapsed (BI=31 and II=17). The final COex average was 0.72ppm. In logistic regression analysis, it was observed that the moderate/severe craving (p=0.0001) was an independent predictor for relapse, with a relative risk of 4.0 (95% CI: 1.5 to 10.7). When comparing the two cognitive behavioural therapy strategies, it was found that fewer II patients relapsed in comparison with BI patients (p=0.001).
Conclusion: The intensive approach was more effective in the treatment of hospitalized patients and only the degree of craving was a significant risk factor for relapse. The inclusion of an innovative technique of cognitive behavioural therapy, easy access and low cost such as the presentation of an educational video proved to be effective in reducing relapse rates in the long term.

INTERVENTIONS IN CARDIOVASCULAR PREVENTION

P5140 | BEDSIDE
Cocoa flavanols improve vascular health: a randomized placebo-controlled study double masked trail in healthy middle-aged subjects

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Background: Cocoa flavanols (CF) increase endothelial function and decrease blood pressure in patients with cardiovascular disease or subjects at increased cardiovascular risk.
Aim: We investigated the primary preventive potential of a dietary CF intervention on vascular health as determined by endothelial function, the Framingham risk model, and vascular age in healthy middle-aged individuals.
Methods: In a randomized, placebo-controlled, double-masked, parallel-group dietary intervention trial, 100 middle-aged (35-60 yrs) male (n=50) and female (n=50) (50-80 yrs), who had no history, signs, or symptoms of vascular disease consumed either a CF-containing drink (450 mg CF) or a nutrient-matched, CF-free control twice daily for 1 month. The primary endpoint was endothelial function (flow-mediated vasodilation [FMD]). Secondary endpoints included plasma lipids and blood pressure allowing the calculation of the Framingham risk scores and pulse wave velocity (PWV) to estimate vascular age.
Results: Following 1 month of daily CF intake, FMD improved in healthy male and female individuals. Furthermore, the subjects blood pressure, total and LDL cholesterol decreased while HDL cholesterol increased leading to decrease in 10 year Framingham risk to develop coronary heart disease (-32%) or cardiovascular disease (-21%), experience a myocardial infarction (-22%) or die from coronary heart (-34%) or cardiovascular disease (-43%). PWV velocity significantly decreased (-0.34 m/s, equivalent to 3.5 years of vascular age). (Clinicaltrials.gov: NCT01799005)
Conclusions: Increasing dietary cocoa flavanol intake improved the most important cardiovascular surrogate parameters providing solid data that underscore the primary preventive potential of dietary flavanols to maintain vascular health.

P5141 | BEDSIDE
Major adverse cardiac events (MACE) and all-cause mortality in levothyroxine substituted individuals with subclinical hypothyroidism: a large cohort study

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Purpose: Subclinical hypothyroidism is associated with a number of cardiovascular risk factors such as hypertension, hypercholesterolemia and diastolic dysfunction, but only limited data exist on long-term outcome of levothyroxine substitution therapy. Therefore we examined effects of levothyroxine substitution treatment on all-cause mortality and major adverse cardiac events (MACE) in patients with subclinical hypothyroidism.
Methods: Patients >18 years consulting their general practitioner from 2000–2009 in Copenhagen, Denmark, who underwent thyroid blood tests, were identified by individual-level linkage of nationwide registries. Only patients with subclinical hypothyroidism (elevated TSH (Thyroid-Stimulating Hormone) with normal FT4 (Free Thyroxine)) at baseline were included. History of thyroid disease, related medication or treatment with lithium, amiodarone and glucocorticoids were excluded. Levothyroxine treatment was only considered if initiated within 6 months from baseline. Incidence Rate Ratios (IRR) of MACE (combined endpoint of non-fatal myocardial infarction, stroke, or cardiovascular death) and all-cause mortality were analyzed using Poisson regression models.
Results: The total cohort comprised 12,212 patients who had subclinical hypothyroidism (mean age 55.2 [SD ± 18.8] years; 79.8% female). Within the first 6 months, 2,452 patients (20.1%) claimed prescription of levothyroxine. The remaining 9,760 patients (79.9%) either initiated levothyroxine therapy later than 6 months after their initial blood test, or did not receive any substitution treatment. During a mean follow-up of 5.0 (SD ± 2.6) years, 1,165 MACE events were observed and 1,566 patients died. MACE rate was 20/1000 person-years (py) among untreated and 17/1000 (py) among levothyroxine treated. Overall mortality rate was 26/1000 person-years (py) and 21/1000 (py) among untreated and levothyroxine treated, respectively. No influence on MACE (IRR 1.02 [95% CI: 0.87–1.19]) and all-cause mortality (IRR 1.02 [95% CI: 0.88–1.17]) was found in patients substituted with levothyroxine.
Conclusions: In patients with subclinical hypothyroidism substitution with levothyroxine does not affect the risk of MACE and all-cause mortality.

P5142 | BEDSIDE
Angiotensin receptor blockers reduce the incidence of malignant tumors in hypertensive patients at high risk of cancer

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Purpose: Whether new onset cancer is reduced by angiotensin II type 1 receptor blocker (ARB) therapy is controversial. The aim of this study was to examine this issue in hypertensive patients.
Methods: Patients treated for hypertension for≥1 year with no previous history of cancer were enrolled into the study from January 2003 to December 2008 and divided into 2 groups (with and without ARBs). Kaplan-Meier time-event curves were used to predict time to onset, and the log-rank test was performed. Incidence rates were calculated using the Cox proportional hazards model with a 95% confidence interval (CI). Sub-group analyses of age, sex, and smoking status were also performed.
Results: Among the 2,313 patients in the ARB group and the 1,375 patients in the non-ARB group, 58 patients in the ARB group (2.51%) and 52 patients in the non-ARB group (3.78%) developed malignant tumors (log-rank test p=0.014). The Cox proportional hazards model revealed a significant decrease in the incidence of malignant tumors in the ARB group (incidence ratio: 0.62, 95% CI 0.43-0.91). In all sub-groups with cancer risk factors, Kaplan-Meier analyses showed that new cancer development was significantly lower in the ARB group than in the non-ARB group (over 60 years p=0.025; male p=0.022; current smoker p=0.003, log-rank test).

The effect of ARB on cancer incidence

	Cancer incidence/n (%)		Log-rank test p-value
	ARB, n=2313	Non-ARB, n=1375	
Current smoker, n=1251	34/811 (4.2)	34/440 (7.7)	0.003*
Non-current smoker, n=2437	24/1502 (1.6)	18/935 (1.9)	0.50
Male, n=2085	46/1346 (3.4)	39/739 (5.3)	0.022**
Female, n=1603	12/967 (1.2)	13/636 (2.0)	0.18
≥60 years, n=2147	47/1332 (3.5)	43/815 (5.3)	0.035**
<60 years, n=1541	11/981 (1.1)	9/560 (1.6)	0.32

ARB, angiotensin receptor blocker. *p<0.01, **p<0.05.

Conclusions: The incidence of malignant tumors was significantly lower in patients treated with ARBs. This phenomenon was more apparent in the high cancer

risk group. These results suggest that ARBs may decrease the occurrence of malignant tumors, especially in those at high risk of cancer.

P5143 | SPOTLIGHT
Artificial neural network modeling using clinical and knowledge features predicts salt reduction behavior

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Purpose: High dietary salt intake is accountable for up to 30% of the prevalence of hypertension. Hypertension in turn is a significant risk factor for hazardous cardiovascular events. The Institute of Medicine (IOM) recommends a salt intake of less than 6g/day/person. Predicting behaviors regarding salt intake habits is vital to guide and focus interventions and increase their effectiveness. We aim to develop an Artificial Neural Network (ANN) statistical based tool that predicts behavior from key knowledge and attitude questions along with clinical data in a high cardiovascular risk population.
Methods: We collected knowledge, attitude and behavior (KAB) data on 115 high risk patients (Coronary Care unit) (mean age: 60.63 SD 15.39 years). A behavior score (BS) was calculated by giving a weight to every answer for the behavior questions from 1 to 4 (unfavorable to favorable) and adding all the weights together. We classified patients into either Favorable Behavior (BS>31), Less Favorable Behavior (B between 26 and 31) or Unfavorable Behavior (B<26) for reducing salt intake. Clinical features (diastolic and systolic blood pressure, pulse, smoking status and medical history of hypertension) that achieved low correlation among each other (R<0.5) were selected for use in the model. Other clinical features which achieved high correlation (R>0.5) with these clinical features were eliminated since they add little information. Starting from a 34-item questionnaire on KAB related to salt intake, a reduced model was developed and included only 8 knowledge questions found to result in the highest accuracy. Accuracy comparison between ANN and regression analysis was calculated using the bootstrap technique with 100 iterations. The reported accuracy is the average correct prediction over all iterations.
Results: ANN based model achieved an accuracy of 62% CI (58%–67%) using knowledge questions only; The statistical model has been implemented in an online calculator that allows the physician to estimate the patient's behavior from a few questions. The physician can fill in clinical only, knowledge only, or a combined input to predict the behavior with 60%, 62%, and 60% accuracy, respectively.
Conclusion: Using ANN modelling that incorporates 8 knowledge questions about Salt intake- in addition to baseline clinical information- we can predict favorable salt reduction behaviors with 62% accuracy. This tool can be used in clinics to guide therapeutic salt reduction interventions in high Cardiovascular risk individuals with reduced effort and time from the healthcare providers.

P5144 | BEDSIDE
Dual antiplatelet therapy in stable patients with coronary artery disease: determinants and impact on prognosis, insights from the coronor study

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Background: The impact of prolonged DAPT in stable CAD patients is debated. Our aims were (1) to assess the proportion of stable coronary artery disease (CAD) patients under dual antiplatelet therapy (DAPT) in real life conditions, (2) the determinants of DAPT prescription and (3) to compare outcomes of patients under DAPT versus those under mono antiplatelet therapy (MAPT).
Methods: Altogether, 3691 patients with stable CAD for at least 1 year (median time of 4 years) were divided in 2 groups according to their antiplatelet therapy regimen at inclusion: patients under MAPT (n=2823) were compared to those under DAPT (n=824). A 1:1 propensity score matching was used to reduce the bias due to group differences.
Results: Interestingly, 824 (22%) patients received DAPT at inclusion. Predictors for long-term DAPT were a shorter delay between the last coronary event and inclusion (lasting for 1 to 3 years), a more diffuse atherosclerosis (persitent angina at inclsuion, multivessel CAD, history of peripheral vascular intervention) and prior drug eluting stent (DES) implantation. Markers for a lower risk of bleeding (age, body mass index) were also predictors. After propensity score matching, the rate of the composite endpoint (death, MI and stroke) at 2 years was strictly similar between patients with or without DAPT: 5.5% versus 5.7% (p=0.886). The rate of BARC ≥3 bleeding was also similar between groups: 1% versus 0.7% in the DAPT and MAPT groups (p=0.601).
Conclusions: Our study reports for the first time that the proportion of patients with stable CAD under long-term DAPT in a comtempory practice is high and around 20%. The major determinants of long-term DAPT were a shorter delay since the last coronary event, markers for a more diffuse atherosclerosis, DES implantation, and markers for a lower risk of bleeding. Of note and even so no increase in major bleeding was observed, our results do not support the prescription of prolonged DAPT.

P5145 | BENCH
A novel potent and selective PPARalpha agonist, K-877, ameriolates the atherogenic profile of fasting and postprandial hypertriglyceridemia in mice

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Fasting and postprandial hypertriglyceridemia (PHTG) is caused by the impaired metabolism of TG-rich lipoproteins and their remnant lipoproteins. Since remnant lipoproteins including VLDL remnants and chylomicron remnants are highly atherogenic, many treatments for improving impaired metabolism of remnant lipoproteins have been investigated in order to prevent atherosclerotic cardiovascular events. In the current study, we have investigated the effect of a potent and selective peroxisome proliferator-activated receptor alpha (PPARα) agonist, K-877, on postprandial metabolism of remnant lipoproteins.
Male C57BL/6J mice were fed a western diet (WD), WD containing K-877 (0.0005%) or WD containing fenofibrate (0.05%) for 4 weeks (n=10/group). Weight gain and dietary intake of all mice were measured, and oral fat loading (OFL) test was performed using olive oil by gavage (17 μL/g body weight) after an overnight fast. Plasma concentrations of TC, TG, FFA and apoB-48 were compared at fasting and during OFL test. Furthermore, lipoprotein profiles of plasma were compared after OFL using high performance liquid chromatography (HPLC) and LPL activities were measured in each group.
Compared with WD, K-877 and fenofibrate groups showed less weight gain but dietary intake was similar. Fasting TG concentrations were significantly lower in K-877 and fenofibrate-treated group than in WD group (WD vs K-877 vs fenofibrate group, 81.0±21.5 vs 32.0±8.7 vs 29.7±8.8 mg/dl; p<0.01 vs WD group), and there were little increase in TG and FFA after OFL in these two groups (incremental area under the curve of TG, WD vs K-877 vs fenofibrate group, 339.7±146.4 vs 56.9±118.1 vs 27.5±33.4 mg*6h/dl; p<0.01 vs WD group). In HPLC analyses, K-877 and fenofibrate significantly decreased the peaks of lipoproteins in the size range of CM, VLDL and HDL in plasma after OFL. Compared with WD group, LPL activities were significantly increased in K-877 and fenofibrate groups. These results suggested that both K-877 and fenofibrate improve PHTG and the accumulation of remnant lipoproteins by increasing LPL activity.
K-877 may attenuate fasting and postprandial hypertriglyceridemia by enhancing LPL activity and reducing weight gain.

P5146 | BEDSIDE
Febuxostat, a xanthine oxidase inhibitor, may improve cardiorenal interaction: a randomized controlled pilot study

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There is growing evidence of an association between high uric acid (UA) levels and cardiovascular disease. However, little data is available about the mechanism by which UA metabolism affects cardiorenal interaction, which leads to cardiovascular disease. Febuxostat, a selective xanthine oxidase inhibitor, was approved in 2012 in our country not only for the treatment of patients with only gout, but also for those with only hyperuricemia. We hypothesized that febuxostat might modify cardiorenal interactions by suppressing the renin-aldosterone system and improving the renal function in hypertensive hyperuricemic patients. We conducted a 6-month, prospective, randomized, open-label study in which we classified hypertensive hyperuricemic patients to either a febuxostat group (n=25) or a control group (n=27). Febuxostat therapy was initiated at a starting dose of 10 mg/day in patients with a serum UA level ≥7.0 mg/dL. The serum UA level of the patients

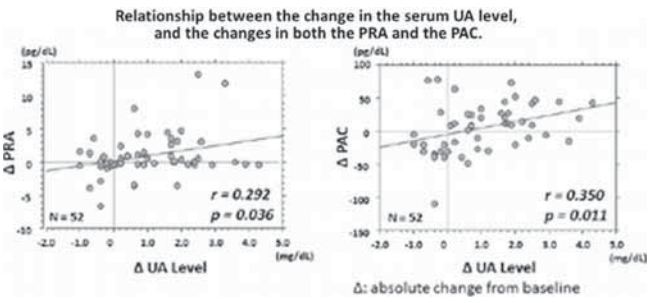

Figure 1

was monitored, and the dose of febuxostat was adjusted to maintain the serum UA level <6.0 mg/dL throughout the course of the study. In the febuxostat group, the plasma renin activity (PRA), plasma aldosterone concentration (PAC), and serum UA level significantly decreased by 33% ($p<0.05$), 14% ($p<0.05$), and 23% ($p<0.0001$), respectively. The estimated glomerular filtration rate significantly increased by 6.0% ($p<0.05$). None of these changes was observed in the control group. Significant positive correlations were observed between the change in the serum UA level, and the changes in both the PRA and the PAC.
Conclusion: These results support the hypothesis that febuxostat might not only reduce the serum UA level, but may also improve cardiorenal interaction. These preliminary findings require confirmation in larger clinical trials.

P5147 | BEDSIDE
Weight loss and reduction of waist size in 362 hypogonadal men with obesity grades I to III upon long-term treatment with testosterone undecanoate (TU): observational data from two registry studies

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Introduction: Numerous studies have reported inverse associations between testosterone and obesity. Obesity seems to have a greater impact on the decline of testosterone with advancing age than age itself.
Methods: From two prospective, cumulative registry studies of 561 hypogonadal men, 362 men with obesity grade I (BMI 30-34.9), grade II (BMI 35-39.9) and grade III (BMI $\geq$40 kg/m^2) were selected. All men received TU injections for up to 6 years. Measures were taken at each three-monthly visit.
Results: Grade I (n=185, mean age: 58.4±8.0 years): Weight (kg) decreased from 101.88±6.2 to 89.34±6.7. These changes were statistically significant for all six years compared to the previous year. Mean change from baseline was -12.55±0.44 kg, percent change from baseline -12.25±5.76%. Waist circumference (cm) decreased from 107.07±7.57 to 97.09±6.95. These changes were statistically significant for five years compared to the previous year and approached significance at the end of six vs. five years. The mean change from baseline was -9.24±0.3 cm. BMI (kg/m^2) decreased from 32.51±1.39 to 28.63±1.92, mean change from baseline -3.99±0.14 kg/m^2. Grade II (n=131, mean age: 60.6±5.6 years): Weight (kg) decreased from 117.02±6.99 to 96.78±7.47. These changes were statistically significant for all six years compared to the previous year. Mean change from baseline was -20.67±0.51 kg, percent change from baseline -17.03±5.02%. Waist circumference (cm) decreased from 114.23±7.51 to 102.52±6.5. These changes were statistically significant for all six years compared to the previous year. Mean change from baseline was -12.29±0.33 cm. BMI (kg/m^2) decreased from 37.39±1.46 to 31.05±2.02, mean change from baseline -6.58±0.16 kg/m^2.
Grade III (n=46, mean age: 60.3±5.4 years): Weight (kg) decreased from 129.02±5.67 to 103.33±4.17. These changes were statistically significant for all six years compared to the previous year. Mean change from baseline -27.15±0.74 kg, percent change from baseline -20.99±3.16%. Waist circumference (cm) decreased from 118.41±5.69 to 106.48±4.91. These changes were statistically significant for all six years compared to the previous year. Mean change from baseline was -12.44±0.36 cm. BMI (kg/m^2) decreased from 41.93±1.5 to 33.62±1.58, mean change from baseline -8.79±0.23 kg/m^2.
Conclusions: All changes were more pronounced with increasing obesity grade. All changes were in a clinically meaningful magnitude and sustainable for the full observation period. TRT seems to be an effective approach to achieve sustained weight loss in obese hypogonadal men, thereby potentially reducing cardiometabolic risk.

P5148 | BENCH
High-dose intravenous N-acetylcysteine prevention of contrast media-induced nephropathy in heart failure: CASIS-HF-A multicenter prospective controlled trial

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Background: Contrast media-induced nephropathy (CIN) is one of the major complications in patients who undergo coronary angiography and percutaneous coronary intervention (PCI). Reduced left ventricular systolic function is an established risk factor for the development of CIN. We investigated the efficacy of prophylactic intravenous high-dose N-acetylcysteine (NAC) for the prevention of CIN in patients with heart failure who were undergoing coronary angiography and/or PCI.
Methods: A total of 134 patients with heart failure were randomized into 2 groups: 68 patients were assigned to NAC plus saline infusion (NAC group: intravenous bolus of 1200 mg of NAC twice daily before and on the day of the coronary procedure plus 0.9% saline 0.5 mL/kg/h 12 h before and 12 h after the procedure) and 66 patients were assigned to saline infusion (Control group: 0.9% saline 0.5 mL/kg/h 12 h before and 12 h after the procedure). The primary end point was the maximum increase in serum creatinine (SCr) level. The secondary end point was the development of CIN after the procedure.
Results: The maximum increase in SCr levels was significantly lower in the NAC group than in the control group -0.005 [-0.10 to 0.10] mg/dL vs 0.04 [-0.04 to 0.10], respectively, (P=0.032). The incidence of CIN was lower in the NAC group than in the control group (5.9% vs 9.1%), but the difference was not statistically significant (P=0.528) (Fig. 1).

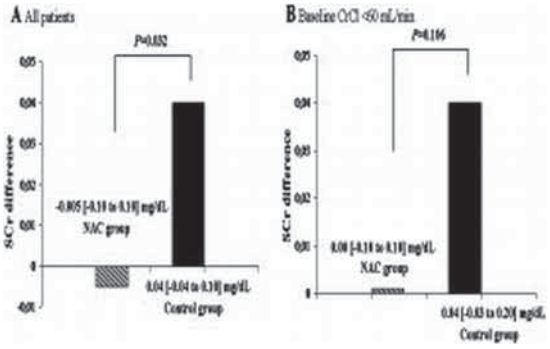

Figure 1

Conclusion: The results of this study suggest that use of intravenous high-dose NAC before coronary procedures may decrease SCr levels in patients with heart failure.

INTERVENTIONS AND OUTCOMES IN CARDIOVASCULAR PREVENTION

P5150 | BEDSIDE
Impact of depressive symptoms on lifestyle management in post-ACS patients

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Purpose: To study the impact of depressive symptoms on lifestyle related risk factors for coronary artery disease.
Methods: We performed a substudy in RESPONSE, a multicenter randomised clinical trial. Patients (18-80 years) were included within 8 weeks after an ACS. Patients were randomised to a nurse coordinated prevention program (NCPP) in addition to usual care (intervention) or usual care alone (control). The intervention consisted of 4 visits within six months, and focused on guideline based risk factor management through medication and lifestyle modification. In a sub study, a subset of patients were screened for depressive symptoms using Beck's depression inventory (BDI) questionnaire at baseline and 12 months. Patients with a BDI score of ten or more were classified as having depressive symptoms. Lifestyle related risk factors were (self reported) smoking, overweight and lack of physical inactivity.
Results: A total of 735 participants were randomised in the main study, 164 of these were screened for depressive symptoms using BDI. Twenty-two patients (13,4%) were classified as depressive (11 in the intervention group) and 116 as non-depressive (55 in the intervention group) Lifestyle risk factors were highly prevalent (table), with significantly more smoking and physical inactivity among patients with depressive symptoms Improvement of lifestyle related risk factors was significantly less among patients with depressive symptoms (table), with no impact of the NCPP compared to control.

Lifestyle risk factors

	Baseline			12 months follow up		
	Non depressive	Depressive	p value	Non depressive	Depressive	p value
Smoking, n (%)	48 (41,1)	14 (63,6)	0,06	24 (20,9)	10 (47,6)	0,01
Overweight, n (%)	90 (77,6)	14 (63,6)	0,18	94 (81,7)	12 (57,1)	0,02
Inactivity, n (%)	49 (42,2)	11 (50,0)	0,64	36 (31,0)	11 (50,0)	0,07

Conclusion: Depressive symptoms are prevalent following ACS and are associated with a higher prevalence of lifestyle related risk factors. In addition, depressive symptoms are associated with less improvement at 12 months. Our findings suggest that screening for depression should precede lifestyle interventions.

P5151 | SPOTLIGHT
The hearthealth trial: improving depressive symptoms and cardiovascular disease risk in the most physically and mentally unhealthy area in the United States

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Purpose: Appalachian Kentucky has the highest rate of mentally and physically

unhealthy days in the America. The prevalence of multiple co-morbid cardiovascular disease (CVD) risk factors is higher among individuals with depressive symptoms living in Appalachia. Our purpose was to determine the effect on depressive symptoms and other CVD risk factors of a self-care CVD risk reduction intervention that included depression management for Appalachians living in a socioeconomically austere environment.
Methods: We enrolled 425 adults (76% women; mean age 58±16yrs) with two or more CVD risk factors and randomized them to an immediate intervention group or a wait-list control group. The intervention consisted of a 12-week self-care risk reduction program focused on addressing environmental and individual barriers to CVD risk reduction. The program included self-care strategies aimed at preventing or reducing depressive symptoms with the ultimate goal of improving heart healthy behaviors. The program targeted lifestyle change with behavioral intervention; drug therapy was not included.
Results: Depression scores were unchanged during the non-intervention wait-list period, but decreased significantly in both groups ($p<0.001$) after the intervention; 18.5% of participants had depressive symptoms prior to the intervention and that was reduced to 7.6% after the intervention (41% reduction in depression). With regard to CVD risk factors, during the wait list control period there were no changes. Following the intervention, these changes were seen: 1) low density lipoprotein (LDL) decreased from a pre-intervention level of 110.5±34.5 mg/dL to 95.8±32.6 mg/dL ($p=0.01$); 2) high density lipoprotein (HDL) increased from 34.5±13.2 mg/dL to 39.8±12.9 mg/dL ($p=0.03$) and in women, increased from 49.6±15.1 mg/dL to a post-intervention level of 55.7±15.0 ($p<0.001$); 3) total cholesterol decreased from 190±38 mg/dL to 180±36 mg/dL ($p<0.001$); 4) pre-intervention, 21% of participants engaged in moderate activity for 30 minutes per day at least 4 days a week, while post-intervention 60% did ($p<0.001$); 5) body mass index pre-intervention was 32.6±7.7 and went down to a post-intervention level of 28.4±7.9 ($p<0.001$). Depression reduction was associated with enhanced CVD risk reduction.
Conclusion: A self-care approach to CVD risk reduction that includes depression prevention and management is effective in a rural population living in a socioeconomically distressed area at high risk for both depression and CVD.

P5152 | BEDSIDE
Resting heart rate and ideal cardiovascular health. The Paris Prospective Study III

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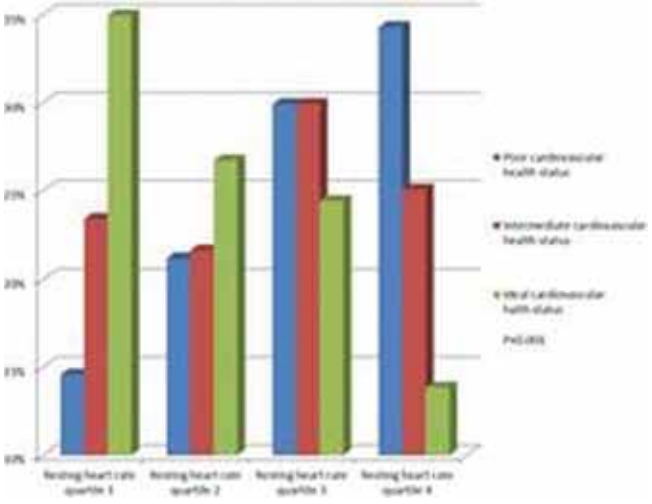
Purpose: Lower resting heart rate (RHR) has been related to lower risk of cardiovascular (CV) disease in large prospective studies. In 2010, the American Heart Association's 2020 Strategic Goals defined a new concept of ideal CV health composed of 7 modifiable health metrics in order to prevent CV disease. We hypothesized that ideal CV health status would be associated with lower RHR.
Methods: We included 5166 men and women aged 50-75 years who enrolled in the Paris Prospective Study III (PPS3) from 2008 to 2011 and who were free of overt CV disease and treatment. The CV health status was defined as poor (0 or 1 health metric), intermediate (2, 3 or 4) and ideal status (5, 6 or 7). RHR was measured at rest after 10 minutes in supine position and categorized in sex specific quartiles. The likelihood of a lower RHR (first quartile) associated with ideal CV health status was explored by logistic regression analysis.



CV health status by RHR quartiles.

Results: Mean age was 58.9 years and 60.6% were men. The median RHR was 61 bpm (IQR: 55, 67) in men and 62 (IQR: 57, 68) in women respectively. The prevalence of ideal and poor CV health status was 13.6% and 14.1% respectively. The prevalence of ideal CV status decreased while that of poor CV health status increased with RHR quartiles ($P<0.001$, see figure). After adjusting for age and sex, participants with intermediate (OR: 1.90, 95% CI [1.51-2.39]) and ideal CV health status (OR: 2.93, 95% CI [2.23- 3.85]) were more likely to have a lower RHR compared with those with poor CV health status respectively.
Conclusion: By showing that ideal CV health status had a three-fold increased odds of having low RHR, the current data support the potential benefit that may be expected through the promotion of primordial prevention of CV disease.

P5153 | BEDSIDE
Evidence-based cost-effective analysis of a school-based electrocardiographic screening system for cardiovascular diseases

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Background: A school-based electrocardiographic screening program has been developed for 1st (6 years old), 7th (12 years old), and 10th (15 years old) graders since 1994. However, evidence-based cost-effective analysis (CEA) of the system was not determined and was not compared with overseas data.
Methods: The model of analysis was a state transmission Markov model. The focus was detection and treatment of long QT syndrome (LQTS) and hypertrophic cardiomyopathy (HCM). The arm was the presence or absence of the screening program. Because a 60% decline in sudden cardiac death in subjects from 5 to 17 years olds was reported between pre- and post-examination periods, preventing death rate was assumed as 60% by the presence of the screening. Prevalence of HCM and LQTS was determined using the data of the screening system. HCM was diagnosed when left ventricular wall thickness was ≥13 mm. LQTS was diagnosed by HRS/EHRA/APHRS Consensus Statement. Five HCM patients of 337,720 six-year-old subjects (1/67,544) were diagnosed and 16 patients of 322,610 twelve-year-old subjects (1/20,163) were diagnosed in 5 areas; prevalence of HCM was estimated to be 1/68,000 and 1/20,000 in 6- and 12-year-old subjects, respectively. Nine patients out of 27,482 six-year olds and 23 of 28,885 twelve-year olds were diagnosed as LQTS: prevalence of LQTS was estimated to be 1/3,000 and 1/1,250 in 6- and 12-year-old subjects, respectively. The data for 15-year olds were not present; prevalence of HCM was estimated to be the same as 12-year olds. Screening of LQTS patients at high school was estimated to be 0, because prevalence of 1/1,250 was higher than that of 1/2,000 in healthy live births in Italy. The precision parameters of the examination (sensitivity, specificity, etc) were referred to a previous work. For cost parameters, Japanese medical fee data in 2013 were used.
Results: The life-years saved by the screening system was 66,879 [person-years], and the cost was $232,000,000. Incremental cost-effectiveness ratio (ICER) was $3,481/person-years, which was less than $41,400.
Conclusion: The cost effectiveness of the electrocardiogram screening program was firstly estimated as $3,481 per person-years ($1 = ~102 yen). The reasons for a low ICER may be a low prevalence of HCM in children and adolescents and low medical costs.

P5154 | BEDSIDE
Blood pressure variability, metabolic profile and cardiovascular risk in 9 eastern european countries: data from the BP-CARE study

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Introduction: Previous studies suggest that blood pressure (BP) variability may exert a predictive role in determining cardiovascular risk. Aim of the present analysis of the BP-CARE study was to evaluate the relationships between BP variability and cardiovascular risk factors in a hypertensive population of Eastern Europe.
Methods: In each subject of the BP-CARE study was calculated the coefficient of variation (CV) of office systolic BP. The population was then divided into quartiles of CV and the differences among quartiles in glucose and lipid profiles, prevalence of previous cardiovascular events, target organ damage (TOD) and BP control were analyzed.
Results: The mean age of the 6425 hypertensive patients was 59.2±11.4 years, the prevalence of males being 49.4%. Individuals in the highest quartile of CV were older (Q1:58.5±11.4 yrs vs Q4:60.3±11.3 yrs, $P<0.001$), with a predominance of males compared to the lowest quartile. Values of body mass index, waist circumference, prevalence of metabolic syndrome, obesity and dyslipidemia did not differ among quartiles, while there was a higher prevalence of diabetes, previous cardiovascular events and resistant hypertension in subjects in the first as compared to fourth quartile (Q1:24.4% vs Q4:27.6%, Q1:57.4% vs Q4:63.9% and

Q1:30.1% vs Q4:32.7% respectively, P<0.05). The 24-hour BP control was lower in hypertensives with greater variability (Q1:31.9% vs Q4:15.8%, P<0.01). Subjects in the highest quartile of CV showed higher total cholesterol and glycaemia than those in the lowest one (Q1:213.0±45.9 mg/dl vs Q4:216.4±50.7 mg/dl and Q1:106.2±35.5 mg/dl vs Q4:109.8±39.1 mg/dl respectively, P<0.05). Glomerular filtration rate was higher in subjects in the lowest quartile of CV than in those in the highest one (Q1:75.9±24.4mL/min/1.73m^2 vs Q4:71.9±22.0mL/min/1.73m^2, P<0.01). The prevalence of TOD was similar among quartiles of CV, while the cardiovascular risk progressively increased from the lowest to the highest quartile of CV (Q1:66.8% vs Q4:71.8).
Conclusions: In the hypertensive population of the BP-CARE study the increase in BP variability is associated with an increase in cardiovascular risk, an unfavorable glucose and lipid profile and a poorer 24-hour BP control.

P5155 | BEDSIDE
Nocturnal respiratory rate predicts non-sudden cardiac death after acute myocardial infarction

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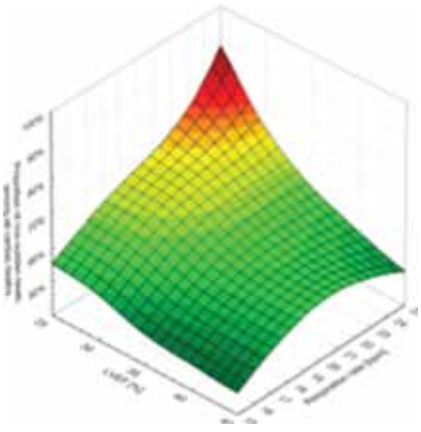
Background: The aim of this study was to develop an algorithm to derive the mean respiratory rate from ECG recordings and to evaluate the power of nocturnal respiratory rate to predict cardiac mortality in survivors of acute myocardial infarction (MI).
Methods: In a cohort of 1538 survivors of acute MI, mean respiratory rate during a nocturnal 6-hour period was determined from Holter recordings. Our algorithm to detect the respiratory rate in an ECG signal based on three parameters (1) QRS amplitudes in individual ECG leads (2) QRS vectors between pairs of ECG leads (3) RR intervals. The respiratory rate ≥18.6/min was considered abnormal. Outcome measures were cardiac death (CD), sudden cardiac death (SCD) and non-sudden cardiac death (N-SCD) at 5 years.
Results: During a follow-up of 5 years, 146 deaths were observed (82 CD, 43 SCD, and 39 N-SCD). In univariable Cox proportional hazards analysis, abnormal respiratory rate was significantly associated with all-cause mortality, CD, SCD and N-SCD (hazard ratios 3.21 (2.32–4.44), 4.63 (2.99–719), 3.13 (1.72–5.69), and 7.40 (3.74–14.59), respectively). In a multivariable Cox analysis which also included left ventricular ejection fraction (LVEF), diabetes mellitus, GRACE score, and COPD, respiratory rate remained significantly associated with N-SCD (hazard ratio 4.56 (2.21–9.43)), but not with SCD. Combination of increased respiratory rate with reduced LVEF identified MI survivors substantially more likely to suffer from N-SCD rather than SCD (Figure).



Conclusion: The nocturnal respiratory rate calculated from Holter ECGs predicts N-SCD in survivors of acute MI.

P5156 | BEDSIDE
Exercise gas exchange response in diabetes: analysis from the EURO(pean) EX(ercise) population-based study

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Background: Diabetes mellitus (DM) is a risk condition that may determine exercise limitation and reduced oxygen consumption (VO2). Diabetic subjects functional characterization with cardiopulmonary exercise testing (CPET) may help to better define cardiovascular (CV) risk and to improve the timing of therapeutic interventions.
Methods: 373 asymptomatic subjects (mean age 59±14 years; male 48%; BMI 28±6 kg/m^2) with different CV risk factors (hypertension 64%, dyslipidemia 48%, smoking 20%, diabetes 14%) underwent a maximal CPET with personalized ramp protocol.
Results: The population was divided into two groups according to the presence of diabetes (Table). Diabetic subjects (n=52) showed a significant lower VO2 (16.3±4.3 vs 20±7.3 ml/kg/min) and O2 pulse (10.2±3.2 vs 11.3±3.9 ml/beat) at peak exercise, a steeper VE/VCO2 slope (27.2±3.5 vs 25.5±3.8) and a reduced heart rate recovery HRR (12±6.5 vs 17±11.5 bpm). A significant difference in the VE/VCO2 slope and peak O2 pulse between the two population was maintained when a correction for confounding factors (BMI, age, gender, prevalence of dyslipidemia and hypertension) was applied.

Table 1

Variables	No DM (n=321)	DM (n=52)	P value
Age (y)	58±14	67±10	0.0000
Male (%)	48.3	51.9	ns
BMI (kg/mq)	27.6±5.5	28.9±5.4	0.008
Peak VO2 (ml/min/kg)	20±7.3	16.3±4.3	0.0000
VE/VCO2 slope	25.5±3.8	27.2±3.5	0.002
HRR (bpm)	17±11.5	12±6.5	0.0000
VO2 at anaerobic threshold (ml/min/kg)	15±5.4	13.3±2.7	0.001
Peak O2 pulse (ml/beat)	11.3±3.9	10.2±3.2	0.038

Conclusions: Asymptomatic DM subjects with normal left ventricular function compared to non-diabetics show an increased VE/VCO2 slope and a reduced peak O2 pulse as a typical phenotype. These findings suggest that a lower increase in cardiac output at peak exercise may play a role. Whether assessment of these variables may improve the risk-related definition and a timely metabolic control in this patients seems to be worth of further investigation.

P5157 | BEDSIDE
Metabolic syndrome has similar explanatory ability in predicting 10-year CVD events as the cluster of risk factors: the attica study

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Background: Whether the metabolic syndrome is a cluster of risk factors without any additive explanatory ability in predicting future cardiovascular disease (CVD) events has been debated by several investigators. We sought to evaluate if metabolic syndrome can better predict future CVD events than the cluster of the common CVD risk factors.
Methods: From May 2001 to December 2002, 1514 men and 1528 women (>18 y) without any clinical evidence of CVD or any other chronic disease, at baseline, living in greater Athens area, Greece, were enrolled. In 2011-12, the 10-year follow-up was performed in 2583 participants (15% of the participants were lost to follow-up). Incidence of fatal or non-fatal CVD (coronary heart disease, acute coronary syndromes, stroke, or other CVD) was defined according to WHO-ICD-10 criteria. Metabolic syndrome was defined according to NCEP ATPIII classification (2005).
Results: The 10-year CVD incidence was 14.3% in men and 9% in women (p<0.001). Multi-adjusted analysis after controlling for age, sex, physical activity, smoking, and dietary habits, revealed that presence of the metabolic syndrome was associated with 1.57-times higher risk of developing a CVD event (95% CI 1.17-2.12). A model that contained the aforementioned set of covariates, as well as the individual features of the syndrome, revealed that only high glucose levels (i.e., >110 mg/dL) were associated with CVD risk; whereas, all other features of the syndrome did not show any significance. Classification analysis revealed that both models had the same correct classification rate, i.e., 85.5%; however, the model that included metabolic syndrome as a single feature had better classification ability as regards the cases, as compared with the analytical model (i.e., 18.5% vs. 15.5%); Moreover the C-statistic (a measure of the predictive accuracy of a model, ranged between 0-1) was equal to 0.804 for the first model that included the metabolic syndrome and equal to 0.808 for the model that included the cluster of the features of the syndrome (p=0.90).
Conclusion: Our data suggest that the accuracy of the metabolic syndrome in predicting 10-year CVD events was similar to the accuracy of the cluster of the common CVD risk factors; whereas, metabolic syndrome as a single feature seems to have better predicting ability in correctly identifying future CVD evens, while the cluster of the components has better classification ability as regards non-events.

P5158 | BEDSIDE
Warfarin discontinuation in patients with unprovoked venous thromboembolism: a large US insurance database analysis

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Purpose: The mainstay of venous thromboembolism (VTE) treatment is anticoagulation, and guidelines recommend therapy for 3 months or longer. This study examined warfarin therapy discontinuation and its risk factors among patients with unprovoked VTE in the US clinical practice setting.
Methods: Adult patients with VTE were identified from the Truven Health Mar-

ketScan insurance database, the largest US claims database. Index date was defined as the date of first VTE diagnosis between 07/01/2006 – 12/31/2011. Patients were required to 1) have ≥2 outpatient VTE diagnosis claims within a 3-week window; 2) have no VTE diagnosis in the 6 months prior to index date; 3) receive warfarin therapy within 10 days of index diagnosis; and 4) have continuous health plan enrollment for 6 months prior and 12 months after index date. VTE was considered as unprovoked if patients did not have reversible provoking risk factors in the 6 months prior and did not have cancer diagnosis or chemotherapy within the 3 months of index date. Warfarin was considered as discontinued if a patient did not have a prescription refilled within 45 days after the ending date of last prescription. Discontinuation rates of warfarin therapy and adjusted hazard ratios (HRs) via multivariate Cox regression were reported.
Results: Of 21,163 eligible patients, 15,463 were diagnosed with deep vein thrombosis (DVT) only (73.1%), 5,027 with pulmonary embolism (PE) only (23.7%), and 673 with both DVT and PE (3.2%). The average duration of warfarin therapy was 5.2 months (SD=3.0). During 1 year follow-up, 21.4% patients discontinued warfarin within 3 months, 42.8% within 6 months, and 70.1% within 12 months. PE versus DVT (HR=0.77), comorbid atrial fibrillation (HR=0.73) and thrombophilia (HR=0.62), and age >40 years (HR=0.86) were associated with reduced risk warfarin discontinuation ($p<0.05$). Alcohol abuse/dependence (HR=1.36), history of cancer (HR=1.13), bleeding (HR=1.07), and catheter ablation (HR=1.10) in the 6 months prior to index date was significantly associated with increased risk for warfarin discontinuation ($p<0.05$).
Conclusions: In the US clinical practice setting, nearly one out of four patients with unprovoked VTE discontinued warfarin therapy within 3 months, and 3 out of 4 patients discontinued therapy within 1 year. Multiple demographic and clinical factors are associated with warfarin therapy discontinuation.

P5159 | BEDSIDE
Incidence of infective endocarditis before and after the 2007 endocarditis prevention guidelines: a population-based study from Qatar (2002-2012)

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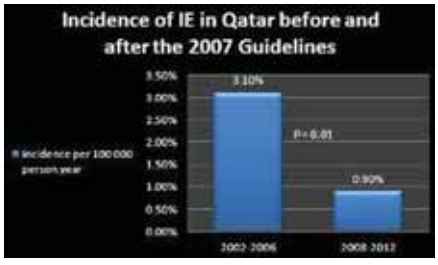
Objectives: The 2007 American Heart Association guidelines for infective endocarditis (IE) prevention markedly restricted the use of antibiotic prophylaxis in certain at-risk patients undergoing dental and other invasive procedures. How that affected the incidence of IE in the developing countries has never been reported. The aim of the current study is to determine if the incidence of IE has changed following adoption of the 2007 guidelines in a real-world population in a Middle-Eastern Country.
Methods: Retrospective analysis of all patients hospitalized with IE in the State of Qatar from 2002 through 2012 was made. Incidence rates per population number per year were compared in the years 2002-2006 (5-years before the guidelines) and 2008-2012 (5-years after the guidelines) with patients hospitalized in the year 2007 excluded to allow time for distribution and application of the guidelines.
Results: We identified 45 cases with IE in Qatar over the 11-year study period 2002-2012. The incidence rate (per 100 000 person-years) during the time interval of 2002–2006 was 3.1 (95% confidence interval, 1.95- 4.40), while during the time interval 2008–2012, the incidence rate was 0.9 (95% confidence interval, 0.5 - 1.4), (P=0.01).



Conclusions: We report a significantly lower incidence of IE following the release of the 2007 IE guidelines in Qatar. Our study represents the first population-based study from a developing country that confirms the safety and effectiveness of these guidelines in IE prevention.

CARDIOVASCULAR EVENTS: PERSPECTIVE, RECOVERY AND END OF LIFE

P5161 | BEDSIDE
Differences in symptom presentation in STEMI patients, with or without a previous history of hypertension; a survey report from the SymTime study group

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Introduction: A variety of factors have been associated with prolonged care seeking behaviour in STEMI patients. Specifically, older age, female gender and different co-morbidities have been found to explain prolonged pre-hospital delay times. However, conflicting data still exist due to the impact of a previous history of hypertension on delay times. We hypothesised that acute symptoms will differ in patients with a previous history of hypertension compared to non-hypertensive STEMI patients.
Methods: SymTime is a Swedish multicentre observational study where STEMI patients admitted to the CCU filled in a validated Swedish questionnaire within 24h from admission. The questionnaire measures how patients with MI describe their symptoms and actions in the pre-hospital phase.
Result: In total, 281 non-hypertensive (53%) and 245 hypertensive (47%) STEMI patients were included (mean age 64+11 and mean age 67+8, respectively). There were significant differences in symptom presentation; chest pain (85% vs. 92%, p=.01, respectively), pain in jaw or teeth were more common in hypertensive patients compared non-hypertensive patients (16% vs. 10%, $p<.05$, respectively) and shoulder (23% vs. 16%, $p<.05$, respectively), and feeling generally ill (20% vs. 11%, p=.01, respectively). After age adjustment, non-hypertensive patients had 1.9 times higher odds (OR 1.94, 95% CI 1.11-3.38) of having chest pain compared to hypertensive patients.
Conclusion: STEMI patients with a history of hypertension, as well as non-hypertensive patients, experience chest pain as the predominantly symptom in the acute phase, but in comparison between groups chest pain is more seldom presented in the hypertensive group.

P5162 | BEDSIDE
Role of nursing information to reduce state anxiety before coronary angiography or PTCA

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Purpose: Patients waiting to undergo a coronary angiography and/or a percutaneous transluminal coronary angioplasty (PTCA), experience high levels of anxiety which present some characteristics typical of this kind of procedure. In cardiac patients it can be dangerous to underestimate the problem of anxiety. Some studies have demonstrated that it worsens the outcome, increasing morbidity and mortality; the aim of this study is to assess if additional nursing information can reduce the level of anxiety felt by patients before undergoing a coronary angiography or a PTCA; the objectives of the study are to: 1) Assess the level of anxiety in people waiting for a coronary angiography or a PTCA; 2) Assess how and in what measure anxiety is modulated; 3) Assess how nursing information influences the state of the patient's anxiety.
Method: Epidemic prospective study, descriptive report, carried out on a sample of 62 patients admitted in an Italian hospital. All the patients had been informed and prepared for the procedure according to standard means (informed consent, talk with a cardiologist), moreover 29 patients received additional nursing information. The following exclusion from the study criteria was applied: age <18, unplanned operation, patients undergoing therapy with anxiolytics, antidepressants, antipsycogens and neuroleptics. The data was collected using STAI (State Trait Anxiety Index).For the general comparison of the score of the two samples (the Informed and the Non-informed) parametric tests (ANOVA and Student's T test) were chosen since the conditions of normality and homoscedasticity of the distribution had been verified. All the analyses were carried out with a level of significance of a = 5.
Results: The results confirm that being subject to such a procedure causes anxiety; females are more anxious than males (p=0.028). Age (p=0.06), education (p=0.82), being accompanied by the usual caregiver (p=0.31) and previous admittance in Cardiology (p=0.07) are not associated with a reduction in anxiety. A reduction in anxiety is associated with previous experience of PTCA (p=0.03) and the presence of additional nursing information (p=0.00); the latter is considered more efficient in reducing anxiety than previous clinical experience (p=0.00).
Conclusions: Nursing information and the way it is modulated are shown to be important variables in significantly reducing anxiety and contributes to making the patient feel more considered as a whole person, aiding the acquisition of a greater control in the events relating to the management of his/her health

P5163 | BEDSIDE
Transitioning towards recovery following ACS (NSTEMI/UA)

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Purpose: The purpose of this study was to investigate the experiences of women with a primary presentation of NSTEMI/UA, in the six to eight week timeframe, after discharge from hospital. The aim was to provide insight in an Irish context and to focus on the mediating impact of a newly-diagnosed disease on their lives. There is increased survival and morbidity across the acute coronary syn-

drome (ACS) continuum. However more adverse outcomes have been reported for women and their needs in rehabilitation have not always been recognised. There is a rising rate of non ST elevated myocardial infarction (NSTEMI) in Ireland; yet there is a dearth of information about women's experiences following NSTEMI and Unstable Angina (UA).
Methods: A naturalistic case study design guided this study. A within-case analysis followed by a cross-case analysis provided meticulous knowledge of each case. Within-methods triangulation captured the depth and breadth of the experiences of thirty women. Data, derived through interviews and participant diaries, were analysed using modified analytic induction which allowed the emergence of theoretical insights.
Results: The women's narratives revealed divergent and yet dominant constructions of disbelief about the onset of ACS (NSTEMI/UA), along with a period of disrupted normality following discharge from hospital. The power of the women's voices to articulate their experiences provides new insight in an Irish context. A number of women had transitioned towards recovery and cardiac rehabilitation was reported positively by those who were attending. However, a critical interpretation of a low rate of referral to cardiac rehabilitation suggests careful consideration is needed in relation to the provision of cardiac rehabilitation programmes and secondary prevention initiatives to meet the needs of women.
Conclusions: This study creates a platform for a wider discourse on the needs of women following NSTEMI and UA. Women may benefit from gender-specific, appropriately timed, and targeted interventions to facilitate recovery and adaptation to living with CHD.

P5164 | BEDSIDE
Women's hearts - fixed and healthy after PCI?

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Purpose: To explore and describe the experiences of women with ischemic heart disease (angina pectoris and myocardial infarction) after Percutan Coronary Intervention (PCI). Furthermore, the study examined changes in daily life affected by the PCI and how women relate to heart-healthy lifestyle.
Methods: Data were collected through qualitative interviews in the respondents' home by using a semi-structured interview-guide reflecting a promotion of health perspective by the International Classification of Function (ICF) model and adherence to heart-healthy lifestyle approach in terms of the Health Belief Model. The interviews lasted for 1-1.5 hours. The data were analyzed in four steps with Malterud's modified version systematic text condensation (STC), based on Giorgi's phenomenological method of qualitative data analysis.
Results: A purposive sample of nine women aged 55-64 were interviewed in 2003. The women were characterized by living alone, low education, incapacitated, sick leave and additional diseases. Risk factors were identified as smoking (n=4), diabetes (n=1), high blood pressure (n=2) and heritage (n=5). Data analysis revealed four main categories: 1. "Experiences in the days before PCI" meaning trivializing cardiac symptoms, undertreated and underdiagnosed, 2. "Experiences with percutaneous coronary intervention" expressed as feeling "fixed" and healthy with few complications, by large being asymptomatic, requesting more information and follow-up, 3. "Experiences in the post-PCI" representing reactions of joy, appreciation of life and lability, consciousness in avoiding stress and focusing boundaries, and 4. "Compliance with heart-healthy lifestyle" in terms of concerning hereditary, symptom management and side effects of medications. Individual risk factors were given little attention, no one stopped smoking and the level of physical activity was generally low. Diet, however, was to a certain degree adjusted to heart friendly advice and recommendations.
Conclusion: PCI was experienced as a quick and uncomplicated treatment which made the women feeling repaired and "fixed". Being free from symptoms after PCI challenges the understanding of ischemic heart disease as a chronic illness. In all, lifestyle was only to a limited extent changed after PCI and the women lived largely as before. Individual health promoting approaches and systematic use of assessment tools, including socio-demographic data and risk assessment factors, may strengthen the focus on women's resources as well as opportunities and needs, to comply with recommendations on heart-healthy lifestyle.

P5165 | BEDSIDE
Patients outcomes and illness perceptions following acute myocardial infarction

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Introduction: Treatment for myocardial infarction is now predicated by clinical presentation and despite the acceptance that primary percutaneous coronary intervention (PPCI) confers greatest benefit in ST elevation myocardial infarction (STEMI), there are concerns in the literature that the speedy treatment and shortened hospital stay may limit patients' understanding of their diagnosis (illness perception) and their motivation for lifestyle change.
Aim: To explore patients' illness perceptions and secondary prevention outcomes following their first myocardial infarction and compare these by treatment modality.
Methods: A prospective, cross sectional design was used to enrol eligible patients into three groups: STEMI treated by PPCI, STEMI treated by thrombolysis and non STEMI. Patients were interviewed during the index admission and after 12 months using the Illness Perceptions Questionnaire and secondary prevention parameters were checked. Data were analysed using standard parametric tests and repeated measures analysis of variance.
Results: Of the 104 patients, 78 provided complete follow up data (PPCI=29, Thrombolysis= 19, NSTEMI= 30) and 62 were males. At baseline the PPCI group had significantly lower personal control (p=0.01) and lower perception of illness consequences (p=0.02) than STEMI patients treated with thrombolysis. Risk factor, demographics and other aspects of illness perception were similar between the 3 groups. At 1 year patients in all 3 groups had reduced their risk factors such as smoking (p=0.001), total cholesterol (0.004) and low density lipids (0.001). Additionally, patients' perception of illness consequences, treatment control and cyclical nature of their illness was significantly reduced across each of the groups. No between group differences in any of these parameters was observed.
Conclusions: Although differences in illness perception were observed in PPCI patients at baseline, these did not persist over time and risk factors improved for all patients irrespective of how they were treated. These data confirm the importance of cardiac rehabilitation and secondary prevention especially for PPCI patients. Further research with a larger sample and longer follow up is indicated to test the association between treatment modality and illness perception and determine any impact on lifestyle change over time.

P5166 | BEDSIDE
Impact of percutaneous coronary intervention for chronic total occlusion in patients with hypertension

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Background: Hypertension is known to be associated with increased adverse clinical outcomes in coronary artery diseases (CAD) patients (pts). The impact of percutaneous coronary intervention (PCI) for chronic total occlusion (CTO) in pts with hypertension is not clear. We compared the 12-month clinical outcomes of pts treated by PCI with optimal medical therapy (OMT) for CTO lesions in pts with hypertension.
Methods: A total of 413 consecutive CTO pts with hypertension divided into 2 groups; one group underwent PCI (PCI group; n=171) and the other group was treated with OMT (OMT group; n=242). Major clinical outcomes were compared between the two groups up to 12 months.
Results: At baseline, the OMT group had higher prevalence of elderly, stroke, peripheral vascular disease, congestive heart failure, left main disease, failed CTO procedure, multi-vessel disease, multi-vessel CTO, RCA-CTO lesion, and more abundant collaterals (≥grade 2), whereas the PCI group had higher prevalence of prior PTCA, current smoker and LAD-CTO lesion. Clinical outcomes at 12 months were similar between the 2 groups except higher TLR and lower trend of mortality in the PCI group (Table). After baseline adjustment by multivariate analysis, there was no difference in 12-month mortality in both groups.

Table. Twelve month clinical outcomes.

Variable.n(%)	PCI (n=170)	Mx (n=208)	P-value
Mortality	7 (4.1)	19 (9.1)	0.055
Cardiac death	4 (2.3)	11 (5.2)	0.146
Non cardiac death	3 (1.7)	7 (3.3)	0.335
Myocadial infaction; MI	5 (2.9)	11 (5.2)	0.259
Q wave MI	4 (2.3)	6 (2.8)	0.749
Non W wave MI	1 (0.5)	5 (2.4)	0.160
Revascularization	17 (10)	18 (8.6)	0.653
TLR	13 (7.6)	3 (1.4)	0.003
TVR	17 (10)	12 (5.7)	0.124
Non TVR	0 (0)	7 (3.3)	0.016
All MACE	24 (14.1)	36 (17.3)	0.398
TLR MACE	17 (10)	15 (7.2)	0.333
TVR MACE	24 (14.1)	32 (15.3)	0.730

Conclusions: In our study, mechanical revascularization by PCI for CTO lesions in pts with hypertension as compared with OMT seems to have no definite benefit in reducing 12-month mortality. Long-term follow up with larger study population will be necessary for further clarification.

P5167 | BEDSIDE
Groin dressing post cardiac catheterization: traditional pressure vs transparent film

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Purpose of the study: To determine the efficacy of using a small transparent non pressure dressing compared with the traditional controlled pressure dressing applied to the femoral artery puncture wound site to maintain haemostasis following cardiac catheterization procedures.
Methods: Design: An experimental design, Randomized Controlled Trial (RCT).
Patients: 80 post cardiac catheterization patients were randomized to have their groins dressed either with pressure dressing (N=40) or Transparent Film Dressing (N=40). Patients ambulated 8 hours after the procedures. Outcome variables were hematoma formation or bleeding, patient discomfort, and nurse-reported

ease of observation of the groin puncture site after the procedure. Five instruments were used for data collection: 1)Demographic and medical data sheet, 2)Hematoma Formation and Bleeding Scale, 3)Skin Integrity Scale, 4)Patient Discomfort and Pain Scale & 5)Nurses Ease of Assessment Scale.
Results: There were no significant differences in base line characteristics and medical data between the two groups. 100% in Transparent Film Dressing (TFD) group vs 55% in pressure dressing group reported feeling very comfortable (p value of 0.003). Hematoma formation was equal in the two dressing groups with no incidence of bleeding complications. Nurses rated the ease of assessing the groin significantly higher for TFD than for pressure dressing (p value of 0.000).
Conclusion: Dressing of the puncture site after cardiac catheterization with TFD was more comfortable than the conventional pressure dressing without any difference in hematoma or bleeding complications. So TFD can be used safely and comfortably after achieving hemostasis.

P5168 | BEDSIDE
It's hard work: a mixed methods study explaining the results of a heart failure self-care skill-building intervention

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Objective: Most of the day to day care for heart failure (HF) is done by the patient at home and requires consistent adherence to complex treatment regimens and vigilance to symptom management. This process of HF self-care requires skill in essential behaviors of self-care maintenance and self-care management. In this mixed method study, we tested the efficacy of a skill-building self-care intervention on HF self-care, knowledge and health-related quality of life (HRQL) at 1- and 3-months and used qualitative data to explain the mechanism of intervention effectiveness.
Methods: Using a randomized control trial design, an ethnically diverse sample (n=75) of patients with HF (53% female; 32% Hispanic, 27% Black; mean age 69.9±10 years) was randomized to the intervention group (IG) or a wait-list control group (CG). A protocol-driven intervention focused on HF self-care skill development delivered in small groups by a health educator. Data were analyzed using mixed (between-within subjects) ANOVA. Intervention sessions were audiotaped and transcribed verbatim. Qualitative data were analyzed using content thematic analysis in order to gain insight into the mechanism of effectiveness of the intervention.
Results: Although there was a significant improvement in self-care maintenance (F=8.33, P=.006), self-care management (F=7.30, P=.01) and knowledge (F=8.00, P=.001) in the IG compared to the CG, there was no improvement in HRQL. The qualitative data revealed that for many the intervention led to an increased awareness "... it woke me up to the fact that I have a problem...". The process of skill building was explained as iterative and reinforcing "it's work... every day... but now I get on that scale and don't pick up the salt... I feel better...". Further, individuals explained that developing skill in self-care was supported by the group format "... I did not even know what to ask... but you realize you are not alone..." and facilitated by the health educator who created a supportive learning environment.
Conclusions: The skill-building intervention improved self-care and knowledge but not HRQL, which may reflect the work required to engage in self-care routinely. Success in practicing self-care reinforced behaviors. These results suggest that ongoing support by experts and peers may help to reinforce self-care behaviors and facilitate ongoing self-care in those who may feel otherwise burdened over time.

P5169 | SPOTLIGHT
Nurses perspectives on discussing prognosis and end-of-life in heart failure patients

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Purpose: Recent Heart Failure (HF) guidelines of the ESC recommend that HF patients should be informed of and invited to discuss prognosis and end-of-life care. At present, the attitude of HF nurses regarding discussing those issues with patients has not been explored. Therefore the purpose of the study was 1) to describe the attitude of HF nurses on discussing prognosis and end-of -life care in HF patients 2) to assess what they experience as barriers and facilitators in discussing these subjects.
Methods: A survey among HF clinics in our country was conducted. A total of 81 HF clinics with 165 HF nurses participated in the study. All nurses filled in a questionnaire about communicating prognosis and end-of-life, including barriers and facilitators they experience in communicating these subjects.
Results: Most of the nurses stated that the physician has the main responsibility to discuss prognosis (63%) or end-of-life (59%) with the patient. However, most of the nurses (93-97%) had discussed these subjects with their patients. Fifty-five % of the HF nurses ever discussed euthanasia with a patient.
Almost 50% of the HF nurses found it more difficult to discuss prognosis or end-of-life care because they were afraid of taking away patients hope, while 27% of nurses stated that patients often would be worried if the nurse initiates a discussion about prognosis. Other reasons that made it more difficult were the unpredictability of the HF illness trajectory (64%) and lack of time to communicate (38%). A good relationship with the patient makes it easier to communicate prognosis and end of life according to 95% of HF nurses. Other factors were questions of the patient (90%) and that something happens to the patient which gives a reason to discuss these subjects (94%).
In total 50% of the nurses reported that they had little or some knowledge in communicating prognosis and 68% in discussing end of life. Only 13% had special education in discussing these themes. Many HF nurses (62-67%) reported that they need further training in these areas.
Conclusion: Many HF nurses reported that it is the main responsibility of the physician to discuss prognosis and end-of-life with HF patients, but many HF nurses discussed the subject with their patients. Shortage of time, the unpredictable cause of the HF trajectory and fear of taking away hope made it more difficult to discuss, while a good relationship and questions of the patient made it easier. Most of the nurses reported a need for more education in communicating prognosis and end of life with their HF patients.

P5170 | BEDSIDE
Should we ask the fear of dying in patients hospitalized for acute coronary syndromes?

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Objectives: Although guidelines recommend the assessment of psychological factors in cardiac patients, the screening of posttraumatic stress disorder (PTSD) after acute coronary syndrome (ACS) is not systematically done in clinical practice. Assessing fear of dying at hospitalization might be a pragmatic approach to identify patients at risk of developing PTSD.
Methods: We enrolled 90 patients hospitalized with a diagnosis of ACS in a Cardiology University Clinic from February to June 2012. At baseline, we collected data on fear of dying, feeling of helplessness, anxiety and coping capacities. One month after discharge, we measured PTSD using the posttraumatic stress scale. Using logistic regression, we estimated age and gender adjusted odds ratios (OR) and 95% confidence intervals (CI) of the associations between baseline psychological factors and the occurrence of PTSD.
Results: 24 patients (26.7%) developed PTSD one month after the ACS event. Patients who developed PTSD reported significantly greater fear of dying (adjusted OR 3.78, 95% CI 1.39-10.31) and helplessness (OR 4.29, 95% CI 1.50-12.22) at the index hospitalization. The fear of dying was associated with high degree of severe anxiety (P=0.002) and maladaptive coping capacities (P value=0.056).
Conclusion: The fear of dying during the hospitalization is associated with the occurrence of PTSD in patients with ACS. A simple question about fear of dying might be useful to identify patients at higher risk for PTSD. Further studies are needed to assess the impact of interventions based on improving coping strategies in those patients.

IMAGING IN HYPERTENSION

P5172 | BEDSIDE
Determination of blood pressure limits combined with non-invasive cardiac computed tomographic findings to obtain good long-term prognosis for major adverse cardiovascular events

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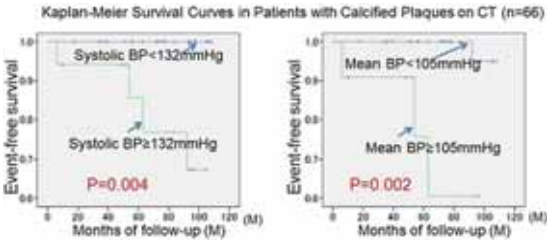
Purpose: To determine blood pressure (BP) indicative of good long term prognosis for major adverse cardiovascular events (MACE), we performed cardiac computed tomography (CT) on patients to evaluate coronary arteries, followed their average of systolic and mean BP during the periods and sought the relationship between BP and CT findings of coronary arteries for the occurrence of MACE.
Methods: A total of 102 consecutive patients (63 male, mean age 64.5±12.3 years) who underwent electrocardiogram gated multi slice CT (Light Speed Ultra 16, GE Healthcare) during 2003-2004 were followed for 78 months (median). 23 had both calcified (CP) and non calcified plaques (NCP); 5 had solely NCP, and 43 had solely CP in coronary arteries. MACE included acute coronary syndrome and cardiac failure.
Results: Three (3%) had a MACE. Receiver operating characteristic curves of



Kaplan Meier Survival Curves

the average of systolic and mean BP during the period revealed best cutoff points of 137 and 105 mmHg for NCP (with and without CP), and 132 and 105 mmHg for CP (with and without NCP), respectively, to differentiate subjects with and without MACE. Kaplan Meier analysis and log rank test revealed nearly significant differences between subjects with NCP (with and without CP) with an average of 1) systolic BP $<$137 and $\geq$137 mmHg, and 2) mean BP $<$105 and $\geq$105 mmHg (both P=0.055); and significant differences between subjects with CP (with and without NCP) with average of 1) systolic BP $<$132 and $\geq$132 mmHg and 2) mean BP $<$105 and $\geq$105 mmHg (both P$<$0.01).
Conclusions: For subjects with CP, NCP, or both of them, BP should be strictly controlled within each limit to prevent occurrence of MACE.

P5173 | BEDSIDE
Aortic distensibility is an independent determinant of retinal arterial remodeling

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Purpose: Microvascular arterial remodelling has been associated with target organ damage and cardiovascular events. Our objective was to assess associations between retinal arterial remodelling calculated using adaptative optics (AO) and ascending aortic function and geometry calculated from Magnetic Resonance (MR) data.
Methods: 57 patients with controlled and uncontrolled primary hypertension and 23 controls underwent AO to measure retinal arteries wall to lumen ratio (WLR) index and a MR exam of the proximal aorta comprising an SSFP cine acquisition acquired in the axial view and during breath-holding, at the level of pulmonary bifurcation perpendicular to the aorta. Ascending aortic diameters and strain were calculated using a custom software, which enables an automated segmentation of aortic Lumen throughout the cardiac cycle. Aortic distensibility (AD) was then calculated as a combination of aortic strain and central pulse pressure (cPP) obtained by tonometry: AD = strain/cPP. Home (hBP) and central Blood Pressure (cBP) were recorded.
Results: Table 1 summarizes patients' characteristics. In univariate analysis, retinal WLR was associated with all BP levels (r2=0.58, p$<$0.0001 for mean cBP) but not with age or any other risk factors. AD was associated with age (r2=0.5, p$<$0.0001) and hBP levels (r2=0.23, p=0.02 for Mean hBP). Finally there was a significant association between AD and WLR, which remained significant, after adjustment for age, gender, hBP, BMI and treatment.

	Controls (mean ± SD) N=23	Hypertensives (mean ± SD) N=57
Age, years	45.1 (12.2)	53.0 (12.1)
Sex ratio (M/F), %	52.1	52.6
Body Mass Index, kg/m^2	24.7 (4.1)	26.3 (4.4)
Systolic hBP, mmHg	119.6 (11.3)	133.7 (15.3)
Diastolic hBP, mmHg	73.0 (7.4)	83.1 (12.1)
Mean hBP, mmHg	88.6 (8.3)	100.3 (12.4)
Wall to lumen ratio	0.276 (.005)	0.325 (.005)
Aortic distensibility, kPa^{-1} 10^{-3}	43.4 (24.3)	21.0 (14.0)

Characteristics of the population.

Conclusion: In our population, AD was a significant correlate of retinal arteriolar remodelling independently of BP levels and age. AO might provide a new insight into macro/microvascular coupling.

P5174 | BEDSIDE
Determinants of ascending aorta dilation in essential hypertension

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Purpose: In chronic essential hypertension (EH), ascending aorta dilation (AAD) is a frequent finding. However, the determinants of this relationship are incompletely understood.
Methods: We studied 780 consecutive newly diagnosed EH (51±13 years, 45% females). Based on the echocardiographic presence of AAD ($>$3.5cm) patients were split in two groups: (AAD, n=230) and (Normal AA, n=550).
Results: Compared to NAA, AAD were older, with higher prevalence of male gender, obesity, metabolic syndrome, alcohol intake and TODs (table). Despite that there wasn't any difference regarding BP levels, AAD consistently had significantly lower heart rate values in all ages. Multivariate logistic regression revealed that age (OR: 1.05 95%CI: 1.04-1.07, p$<$0.001), male gender (OR: 2.3, 95%CI: 1.6-3.5, p$<$0.001), BMI (OR: 1.07 95%CI: 1.03-1.11, p=0.001), alcohol consumption (AC) (OR: 2.01, 95% CI: 1.04-3.9, p=0.038) and heart rate (OR: 0.98 95% CI: 0.97-0.99, p=0.03) are independent predictors of AAD. Moreover, we found a significant interaction between male gender and alcohol consumption (males with moderate AC OR: 1.9, 95%CI: 1.2-3.3, p=0.008, males with heavy AC: OR: 3.3 95%CI: 1.7-6.4, p$<$0.001).

	NAA	AAD	p value
Age, yr	49±13	56±11	$<$0.001
Male gender,%	50.6	64.3	$<$0.001
BMI, kg/m^2	28±5	29±5	0.002
Alcohol: light/moderate/heavy	85.2/10.3/4.5	71.4/18.8/9.8	$<$0.001
PWV, m/sec	8.1±1.7	8.7±1.8	$<$0.001
Ascending aorta systolic–diastolic diameter difference, mm	0.15 (0.1–0.27)	0.19 (0.1–0.3)	0.026
LVMi (indexed to height$^{2.7}$)	39±9	43±10	$<$0.001
LAVI max	26±8	29±8	$<$0.001
LV diastolic dysfunction, %	58.9	76.5	$<$0.001
Carotid IMT, mm	0.69±0.15	0.71±0.14	0.007
Office/24hr/Day/Night HR, bpm	80±12/75±9/78±9/66±9	75±12/71±8/74±9/63±7	$<$0.001

Conclusions: Ascending aorta dilation is already present in one third of newly diagnosed EH patients. Older age, male gender, high alcohol intake and BMI are independent predictors of this condition, with increased heart rate to possess beneficial effects, probable due to diminished stroke volume and cyclic aortic expansion.

P5175 | BEDSIDE
Clinical impact and characteristics of coronary artery tortuosity

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Introduction: In the heart coronary tortuosity (CT) is often observed during coronary angiography (CA). Sometimes it is described in patients with Angina (AP) undergoing CA that turn out to have no coronary arteriosclerosis. In this population CT is often associated with reversible myocardial perfusion defects and a decreased coronary flow reserve. However, the etiology and clinical impact of CT are still undetermined.
Methods: To address this issue we evaluated 177 consecutive patients who were admitted to a cardiological center between 2000 and 2007 for further evaluation of dyspnea or AP by CA, which however did not reveal any evidence of coronary artery disease or structural heart disease. For a quantitative analysis of CT in coronary angiograms a tortuosity index (TI=total length of coronary artery/ shortest length of coronary artery) was calculated. A correlation of TI with patients' characteristics and hemodynamic parameters was performed. To further assess symptomatic and pathophysiological correlations we analyzed the severity of TI in subgroup populations: AP (n=113) vs. non-AP (n=64) and hypertensive patients (HP) (n=90) vs. non-HP (n=87).
Results: No difference in CT severity between AP vs. non-AP was found. However, more pronounced CT was observed in HP. In univariate analysis we found a positive correlation of CT with age (r=0.26), height (r=0.21), number of antihypertensive agents (r=0.27), left ventricular systolic pressure (r=0.31), aortic systolic pressure (r=0.29) and aortic mean pressure (r=0.23). CT severity did not correlate with severity of NYHA class.
Conclusion: Our results suggest that CT may be a manifestation of arterial hypertension. However, it is not associated with cardiac symptoms like AP or dyspnea.

P5176 | BEDSIDE
Association of cystatin C with global left ventricular longitudinal strain in hypertensive patients

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Purpose: Hypertension is one of the most common entities leading to cardiac dysfunction. The impact of abnormal renal function on left ventricular (LV) function in patients with hypertension is not fully understood. We tested the hypothesis that cystatin C is associated with subclinical systolic abnormalities of LV function assessed by speckle-tracking global longitudinal strain (GLS) in hypertension.
Methods: The study population consisted of 90 hypertensive patients without history of diabetes mellitus, coronary heart disease or heart failure and 20 age-matched controls. LV structure and function were assessed by conventional echocardiography and two-dimensional speckle-tracking imaging. We measured possible biomarkers of renal and LV conditions included serum cystatin C, urinary albumin-creatinine ratio (ACR), and plasma B-type natriuretic peptide (BNP).
Results: In the hypertension group, mean GLS was significantly reduced (-18.5±2.7% versus -20.3±1.7%, p$<$0.01) and mean cystatin C level was increased compared with controls (1.00±0.22 mg/L versus 0.85±0.26 mg/L, p$<$0.01). GLS significantly correlated with LV mass index, LV systolic diameter, interventricular septum thickness, and posterior wall thickness (r=0.321, r=0.328, r=0.336 and r=0.387; p$<$0.01: respectively). Serum cystatin C levels were categorized into quartiles (quartile I, 0.66 to 0.84 mg/L; quartile II, 0.85 to 0.94 mg/L; quartile III, 0.95 to 1.00 mg/L; quartile IV, 1.01 to 1.82 mg/L). Age was higher and GLS was reduced in the highest quartile compared with the lowest quartile of cystatin C levels (69±8 yrs. versus 59±11 yrs., p$<$0.01; -17.5±2.4% versus -19.1±2.7%, p$<$0.05: respectively). In multiple regression analysis adjusting for age, ACR, BNP, systolic blood pressure and diastolic blood pressure, cystatin C levels and LV mass index remained significantly associated with GLS (β = 0.246, p$<$0.05; β = 0.258, p$<$0.01: respectively).

Conclusion: Increased levels of cystatin C were related to reduced GLS. This suggests that impaired renal function is associated with subclinical systolic abnormalities of LV function in hypertension.

P5177 | BEDSIDE
Predictors of new-onset atrial fibrillation in essential hypertensives. Left atrial size is the one that matters

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Purpose: The aim of our study was to compare the predictive role of structural heart adaptations,as determined either by left atrium diameter (LAD) or by left ventricular massindex (LVMI), for the incidence of new-onset atrial fibrillation (AF).
Methods: We studied 2.452 hypertensive patients (aged 57.7±11 years, 50% males) without history of AF episodes for a median period of 41 months (IQR 28-60 months). All subjects had at least one visit annually and at entry underwent laboratory examination and complete echocardiographic study including left ventricular diastolic function evaluation by means of transmitral flow (E, A, E/A ratio) and tissue Doppler imaging (Em, Am). End-point of interest was new-onset AF.
Results: The incidence of new-onset AF over the whole follow-up period was 2.5% (31 patients with paroxysmal AF and 20 patients with permanent AF). Patients with new-onset AF compared to those without were older (by 8.7 years, $p<0.001$) and exhibited at baseline higher office pulse pressure (by 5.3 mmHg, p=0.011), greater duration of hypertension (by 2.9 years, p=0.018), left ventricular mass index (99.4±25 vs. 88.8±21 g/m^2, p=0.005) left atrium diameter (40.8±4.6 vs. 37.9±4.8 mm, $p<0.001$), increased E/Em (12.7±4.9 vs. 10.4±3.9, p=0.003)and decreased creatinine clearance (78.9±26.7 vs. 93.7±30.9ml/min, p=0.001)while no difference was observed with respect to gender and body mass index. Multivariate Cox regression analysis revealed that age (HR 1.075, $p<0.001$) and LAD (HR 2.613, p=0.001) turned out to be the only independent predictors of new-onset AF. Based on ROC analysis LAD>38.95mm predicted new-onset AF with sensitivity 76.5% and specificity 56.7%.
Conclusions: Uncomplicated hypertensives with new-onset AF are characterized by a greater prevalence of structural and functional heart adaptations.However, only older age and enlarged LA sizeturned out to predict new-onset AF in the setting of essential hypertension.

P5178 | BEDSIDE
The prognostic value of oxygen kinetics during early recovery after exercise in hypertensive patients with impaired coronary flow reserve

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Purpose: The period of early recovery after exercise is characterized by a rapid payback of the oxygen debt incurred during exercise which in turn reflects normal circulatory function. Hypertension may be accompanied by impaired coronary microcirculation. We hypothesized that oxygen consumption (VO2) during exercise as well as its decline during the first minute of recovery after exercise will be impaired in hypertensive patients with reduced coronary flow reserve.
Methods: Eighty (80) non-diabetic, recently diagnosed and well-controlled hypertensive patients (mean age 51+11 years, 55 men) underwent a ramp symptom-limited cardiopulmonary exercise test (CPET) on a bicycle ergometry. We evaluated exercise parameters (work load, O2 pulse and VE/VCO2 slope) as well as oxygen kinetics during exercise (peak oxygen consumption [peak VO2]) and early recovery period (slope of VO2 decline during the first minute of recovery, VO2rec). Coronary flow reserve, which was estimated before CPET, was measured by means of color-guided Doppler echocardiography at the distal tract of the left ascending coronary artery after adenosine infusion (140 mg/kg/min). The study group was divided according to CFR values to group A (n=57, normal CFR>2) and group B (n=23, impaired CFR<2.0).
Results: No significant differences were found between groups regarding age, body mass index and systolic and diastolic blood pressure at rest. All patients completed successfully the exercise test without ECG signs or symptoms of myocardial ischemia. Regarding total population, VO2rec was strongly related with peak VO2 (r=0.72, $p<0.001$), work load (r=0.70, $p<0.001$), O2 pulse (r=0.70, $p<0.001$) and VE/VCO2 slope (r= -0.20, $p<0.05$). We found that patients in group B had lower work load (146+46 vs. 122+38 watts, $p<0.05$), peak VO2 (2053+570 vs. 1798+455 ml/min, $p<0.05$) while VO2rec was significantly slower (816+374 vs. 634+258, $p<0.01$).
Conclusions: Hypertensive patients with impaired coronary microcirculation exhibit impaired peak exercise parameters (work load, oxygen consumption and oxygen recovery). Cardiopulmonary exercise test may be a useful tool in cardiovascular risk estimation in hypertensive population.

P5179 | BEDSIDE
Reduced coronary flow reserve is related with impaired Endothelial Glycocalyx in low cardiovascular risk patients with newly diagnosed arterial hypertension

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Background: Aortic stiffness and coronary flow reserve are considered valuable indices of subclinical damage in hypertensive patients offering to cardiovascular risk estimation. The integrity of endothelial glycocalyx plays a vital role in vascular permeability, inflammation and elasticity. We aimed to explore the relationship between coronary flow reserve, endothelial glycocalyx and aortic stiffness in patients with newly diagnosed essential hypertension.
Methods: We studied 58 patients with newly diagnosed and never treated essential hypertension (mean age 48+10 years, 40 males). We performed carotid-femoral artery pulse wave velocity (PWV) in order to evaluate aortic stiffness. Since PWV<10 m/sec was considered as normal, patients were divided in Group A (PWV<10 m/sec, n=15, mean age 46+7 years) and Group B (PWV>10 m/sec, n=43, mean age 49+10 years). Coronary microcirculation (CFR) was estimated by echocardiography. Increased perfusion boundary region (PBR) of the sublingual arterial microvessels (ranged from 5-25 micrometers) using Sideview Darkfield imaging (Microscan, Glycocheck) was measured as a non-invasive accurate index of reduced endothelial glycocalyx thickness.
Results: No significant differences were found within groups regarding age, BMI, smoking habit, PWV, PBR (ranged from 5-25 micrometers) and CFR. However, Group B patients had increased systolic and diastolic blood pressure and pulse pressure in office and 24h ABPM measurements. In Group A, CFR was related with PBR5-25 (r=0.60, p=0.01), PBR10-19 (r=0.61, p=0.01) and PBR20-25 (r=0.56, $p<0.05$). No such relationship was shown in Group B patients.
Conclusions: This is the first study showing an existing relationship between reduced coronary flow reserve and endothelial dysfunction, represented by endothelial glycocalyx thickness, in low cardiovascular risk patients. This relationship which may separate patients with intermediate cardiovascular risk, is lost in patients with more severe hypertension as expressed by higher blood pressure levels and impaired aortic stiffness. Further studies are needed to confirm our results and establish endothelial glycocalyx measurement as a valuable tool in cardiovascular risk estimation.

P5180 | BEDSIDE
New inflammatory markers in preeclampsia: echocardiographic epicardial fat thickness and neutrophil to lymphocyte ratio

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Purpose: Increased epicardial fat thickness (EFT) has been proposed as a new cardiometabolic risk factor. The neutrophil/lymphocyte ratio (NLR) has predictive and prognostic value in several cardiovascular diseases. The aim of this study was to explore the association between EFT and NLR in patients with preeclampsia.
Methods: 108 pregnant patients with a mean age of 30.6±6.3 years were included in the study. Patients were divided into 2 groups based upon the presence of preeclampsia. All participants underwent transthoracic echocardiography imaging and complete blood counts were measured by an automated hematology analyzer. Statistical analysis was performed using the Chi-square, Mann-Whitney U, correlation and logistic regression tests, and ROC analysis.
Results: The mean EFT value of the preeclampsia group was significantly higher than the control group (6.9±0.6 vs 5.6±0.6; $p<0.001$, respectively), and the NLR value of the preeclampsia group was also significantly higher than the control group (7.3±3.5 vs 3.1±1.1; $p<0.001$). Multivariate analysis showed that increased levels of NLR and echocardiographic EFT are independent predictors of preeclampsia. In the receiver operating characteristic analysis, a level of EFT ≥6.2 mm and NLR ≥4.1 predicted the presence of preeclampsia with 77.8% sensitivity, 79.6% specificity and 83.3% sensitivity, 81.5% specificity, respectively.

Table 1. Multivariate logistic regression analysis to assess predictors of preeclampsia

	Odds ratio	95% CI	P value
EFT	12.340	2.190–69.530	0.004
MPV	1.596	0.734–3.471	0.238
NLR	2.740	1.354–5.544	0.005
Urea	1.157	0.999–1.340	0.051
Triglyceride	1.011	0.997–1.025	0.133
LVMI	0.985	0.949–1.023	0.443

Conclusions: Unlike many other inflammatory markers and bioassays, NLR and echocardiographic EFT are inexpensive and readily available biomarkers that may be useful for risk stratification in patients with preeclampsia.

P5181 | BENCH
Dipeptidyl peptidase 4 inhibition ameliorates hypertension via normalizing preload through the RAAS axis

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Purpose: DPP4 inhibitors have attracted rising attention regarding their pleiotropic effects on cardiovascular system. Several reports suggested vasorelaxant effects of DPP4 inhibition, namely, anti-hypertensive effect of incretine GLP-1 (Nat Med 2013) or link between DPP4 and angiotensinI-converting enzyme (ACE) regarding angiogedema (Hypertension 2009), however, its role in hypertension remains uncertain.
Methods: Spontaneously hypertensive rats (SHR; 10 w/o male) and its counterpart Wistar-Kyoto (WKY) were treated with teneligliptin (TEN; 10mg/kg/day p.o., 4 wks) (SHR-TEN and WKY-TEN) or vehicle (CON). Cardiac function and blood pressure was analyzed using echocardiogram and cardiac catheterization. Molecular mechanisms were examined in each heart, aorta, and blood specimen.
Results: SHR-CON exhibited increase in heart and body weight (BW) ratio, which was attenuated by TEN. Of note, TEN reduced lung weight and BW exclusively to SHR with concomitant normalization of its elevated BNP level, suggesting TEN may reduce preload via ameliorated pulmonary congestion. Systolic and diastolic blood pressure (SBP and DBP) were higher in SHR-CON (in mmHg; 201±16 and 134±15) than WKY-CON (105±6 and 79±4). TEN reduced both SBP and DBP of SHR (141±17 and 96±6). In contrast, TEN had no effects on BP of WKY. TEN attenuated cardiac hypertrophy of SHR-CON. There was no difference in ejection fraction and LV diameter among all groups. Maximum dP/dt (maxdP/dt) of SHR-CON was elevated (in mmHg/sec; 10452±539) compared to WKY-CON (5739±599), which was reduced by TEN (SHR-TEN; 8033±656) without affecting heart rate, consistently suggesting TEN reduced preload in SHR (because the determinants of maxdP/dt are heart rate and preload). Minimum dP/dt was elevated in SHR-CON, which was ameliorated by TEN; however, there was no difference in other diastolic indices. DPP4 activity was 1.5-fold higher in SHR-CON than WKY-CON, which was suppressed by TEN. Circulating angiotensin 2 (AT-II) was elevated in SHR-CON compared to WKY-CON. TEN reduced AT-II level both in SHR and WKY and TEN modulated ACE activity in vitro. In contrast, the circulating vasorelaxing peptide ANP and the Akt/eNOS signaling in each aorta remained unaffected by TEN.
Conclusions: DPP4 inhibition with TEN ameliorates pathological hypertension and related hyperkinetic cardiac stress by amelioration of preload though the reduction of ACE/ATII axis, a potent vasoconstrictor that increases the retention of sodium and water. Our data suggest a novel link between DPP4 and RAAS pathway.

GENETICS IN HYPERTENSION

P5183 | BEDSIDE
Genetic predisposition of essential hypertension. a prospective study

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Objective: Essential hypertension is a multifactorial disease which involves environmental, genetic and other factors. However, few data exist in the field of genetics. As part of a research program of the NIH in U.S. we examined the role of various genes in essential hypertension, in African-American, Caucasian-American and Greek families.
Design and method: We prospectively studied 1474 individuals from 128 families with a history of hypertension. From this sample, 273 men aged 58±8 years and 286 women aged 63±6 years had essential hypertension. DNA samples were obtained from 410 hypertensive individuals, and created sibling pairs of hypertensive patients.
Results: Two markers on chromosome 17 were associated with increased blood pressure in the Caucasian population. PNMT gene was correlated with essential hypertension in African-Americans but not in Caucasians while there was a significant association of single nucleotide polymorphisms with all groups. In addition, there was a higher diversity of genome and A2B receptor locus and lower linkage disequilibrium in African-Americans compared to Americans and Greeks Caucasians.
There is a hereditary predisposition in the development of hypertension. The presence of maternal hypertension was more frequent in Afro-Americans and Greek hypertensive patients (81,7%, 84,8%,) and less frequent in American hypertensive patients (65%). Te presence of paternal hypertension seems to influence less the incidence of arterial hypertension in Afro-Americans, Greek and American hypertensive patients (50%, 48,3% and 44,9% respectively).
Conclusions: Although there was a correlation of genetic factors with essential hypertension, we couldn't found a gene responsible for the development of arterial hypertension. The role of parents in the development of essential hypertension deserves further examination.

P5184 | BEDSIDE
The study of polymorphism of endothelial no-synthetase gene in arterial hypertension with metabolic syndrome

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Arterial hypertension and metabolic syndrome are closely associated with endothelial dysfunction and form pathogenic "vicious circle". The endothelial dysfunction is more expressed in patients with arterial hypertension in combination with metabolic syndrome. One of the mechanisms of endothelial dysfunction is a competitive suppression and/or reduction in the activity of endothelial NO-synthetase. At present time the impact of polymorphisms T(-786)C and G894T of eNOS gene on the formation of endothelial dysfunction are actively studied in different cardiovascular diseases.
The purpose of the research: analysis of the distribution of genotypes and alleles of polymorphisms T(-786)C and G894T of eNOS gene and features of these polymorphisms in patients with arterial hypertension in the presence and absence of metabolic syndrome in population of the southern region of ou country.
Materials and methods: 58 patients with arterial hypertension and metabolic syndrome were examined and formed the basic group, and 54 patients with arterial hypertension without the metabolic syndrome, which formed the control group. The presence of metabolic syndrome was defined according to the criteria of IDF 2006. Analysis of polymorphic markers of eNOS gene was performed by polymerase chain reaction in conditions of international medical laboratory "Synevo".
Results and discussion: The frequency of T allele and "normal genotype" TT of polymorphism T(-786)C and G894T of eNOS gene in the group of patients with arterial hypertension and metabolic syndrome (62,4% and 44,1%) respectively, and without the metabolic syndrome (63,5% and 46,2%, p>0,05) respectively, exceeded the frequency of the allele C and genotype CC in the surveyed groups, the presence or absence of metabolic syndrome did not significantly impact on the allocation of frequencies in the studied population. In the group of patients with arterial hypertension and metabolic syndrome T allele and "pathological genotype" TT of polymorphism G894T of eNOS gene were observed significantly more often (67,6% and 46,2%, p<0,01) respectively, compared with patients with arterial hypertension without metabolic syndrome in the studied population.
Thus, the major occurrence of "pathological genotype" TT and T allele of polymorphism G894T of eNOS gene with concomitant metabolic syndrome may explain the genetic determinism of more expressed endothelial dysfunction in patients with arterial hypertension and metabolic syndrome, compared with patients without metabolic syndrome in population of the southern region of our country.

P5185 | BEDSIDE
Association of a polymorphism of the transcription factor 21 gene (TCF21) with hypertension in Japanese individuals

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Purpose: Various loci and genes that confer susceptibility to coronary heart disease (CHD) or myocardial infarction (MI) have been identified for Caucasian populations by genome-wide association studies (GWASs). Given that hypertension is a major risk factor for CHD and MI, we hypothesized that some polymorphisms might contribute to the genetic susceptibility to CHD or MI through affecting the susceptibility to hypertension. The purpose of the present study was to examine a possible association of hypertension in Japanese individuals with 15 polymorphisms identified as susceptibility loci for CHD or MI in the previous GWASs.
Methods: Study subjects comprised 5460 Japanese individuals (3348 subjects with hypertension, 2112 controls) who visited the participating hospitals between 2002 and 2012. The subjects with hypertension either had a systolic blood pressure (BP) of ≥140 mmHg or diastolic BP of ≥90 mmHg (or both) or had taken antihypertensive medication. The control individuals had systolic BP of <140 mmHg and diastolic BP of <90 mmHg and had no history of hypertension or of taking antihypertensive medication. Genotypes of polymorphisms were determined by the multiplex bead-based Luminex assay. To compensate for multiple comparisons, we adopted the criterion of a false discovery rate (FDR) of <0.05 for statistical significance of association.
Results: Comparisons of allele frequencies by the chi-square test revealed that rs12190287 (G→C polymorphism) of the transcription factor 21 gene (TCF21) was significantly (P=0.0032, FDR = 0.0485) associated with hypertension. Multivariable logistic regression analysis with adjustment for age, sex, body mass index, and smoking status revealed that rs12190287 was significantly (P=0.0014; odds ratio, 1.21; recessive model) associated with hypertension with the C allele representing a risk factor for this condition. Comparisons of allele frequencies by the chi-square test revealed that rs1122608 (G→T) of SMARCA4 (P=0.0143, FDR = 0.0806) and rs9369640 (A→C) of PHACTR1 (P=0.0161, FDR = 0.0806) were also related to hypertension. Multivariable logistic regression analysis with adjustment for covariates revealed that rs1122608 of SMARCA4 (P=0.0305; odds ratio, 0.86; dominant model) and rs9369640 of PHACTR1 (P=0.0119; odds ratio,

0.82; dominant model) was significantly (P<0.05) associated with hypertension, with the minor T and C alleles, respectively, being protective against this condition.
Conclusions: The rs12190287 (G→C polymorphism) of TCF21 may be a susceptibility locus for hypertension in Japanese individuals.

P5186 | BEDSIDE
Risk genes of hypertension: results from Kaunas cohort study in Lithuania

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Purpose: Clinical and experimental studies have demonstrated a major role of the renin-angiotensin system (RAS) in hypertension. Polymorphisms of angiotensinogen (AGT rs699), angiotensin II type 1 receptor (AGTR1, rs5186), and angiotensin converting enzyme (ACE, rs4340) genes have been extensively studied in association with hypertension, however, findings are conflicting. Among new identified loci for blood pressure and hypertension there are genes encoding adrenomedullin (ADM, rs7129220), a plasma membrane calcium/calmodulin dependent ATPase (ATB2B1, rs2681472) and a beta-2 subunit of voltage-gated calcium channel (CACNB2, rs12258967). The objective of the present study was to assess the contribution of gene polymorphisms to blood pressure (BP) in the Kaunas cohort study.
Methods: Study subjects were participants of Kaunas cohort study started in 1977. At the time of the baseline survey the participants were 12-13 years age old. A total of 507 subjects (64.4% of eligible sample) participated in the 35-year follow-up in 2012 being 48-49 years old. Health examination involved measurements of BP, anthropometric parameters and interview about health behaviours. Single nucleotide polymorphisms (rs699, rs5186, rs7129220, rs12258967, rs2681472, rs4340) were analyzed by real-time and conventional polymerase chain reactions.
Results: Mean values of systolic BP were highest in boys with AGT TT genotype. In girls, the CACNB2 GG genotype carriers had a significantly lower level of diastolic BP than CACNB2 CC genotype carriers. Girls with ADM genotype AA had highest levels of systolic and diastolic BP. The linear regression analysis showed that AGT genotypes were associated with systolic BP in boys. The presence of CACNB2 GG genotype contributed negatively to diastolic BP, while ADM AA genotype was positively related both to systolic and diastolic BP in girls. After adjustment for BMI, alcohol consumption, salt intake and physical activity, the odds ratios (OR) of having hypertension in middle age women with AGT TT genotypes were higher compared to AGT MM genotype carriers (OR=2.31; 95% confidence interval: 1.01-5.29).
Conclusions: The associations between analysed gene polymorphism and blood pressure differ by gender in Kaunas cohort study.

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The burden of hypertension in china in the 21st century: findings from the china kadoorie biobank study of 0.5 million chinese adults

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Purpose: Elevated blood pressure is well established as one of the most important modifiable risk factors for CVD, but relatively little is known about the detection, treatment and control rate of hypertension in China during the recent decade, and the relevance to them of season.
Methods: We examined the prevalence, awareness, treatment and control of hypertension in 500,0000 men and women from 10 regions of China that were examined in 2004-2008 for the China Kadoorie Biobank study. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) and the proportions with hypertension (SBP ≥140 mmHg or DBP ≥90 mmHg or treated with antihypertensive medication) were calculated by age, sex and season.
Results: Mean levels of SBP increased linearly with age by 3.6 mmHg per decade in men and by 7.7 mmHg in women. Likewise, mean DBP increased with age until 55 years, but declined thereafter. Mean levels of SBP and DBP were highest in winter, lowest in summer and intermediate in spring and autumn. Overall, 34% had hypertension, of which 34% were aware of their diagnosis, 13% were treated and 4% were adequately controlled (ie, had SBP <140 mmHg and DBP <90 mmHg; 31% of treated individuals). The proportions that were diagnosed and controlled were much lower in winter than in summer (winter: 28% aware, 11% treated, 2% controlled; summer: 41% aware, 16% treated, 6% controlled).
Conclusions: Radical strategies are required to reduce the enormous burden of undiagnosed and untreated and uncontrolled hypertension in China. Moreover, seasonal variation in blood pressure should be considered in the clinical management of hypertension.

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

P5189 | BEDSIDE
Initial results of balloon pulmonary angioplasty for patients with chronic thromboembolic pulmonary hypertension

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Purpose: Chronic thromboembolic pulmonary hypertension is defined as pulmonary arterial hypertension with persistent pulmonary perfusion defects and is associated with a poor prognosis if untreated. Although surgical pulmonary endarterectomy (PEA) is a potential cure for "central type" of chronic thromboembolic pulmonary hypertension, there is no effective treatment for patients with "peripheral type" or extremely high risk for PEA. Recently, balloon pulmonary angioplasty (BPA) has been introduced as a therapeutic approach for patients with peripheral type of this disease. The purpose of this study was to investigate the efficacy of BPA for the treatment of inoperable patients with chronic thromboembolic pulmonary hypertension.
Methods: Ten consecutive patients (2 men and 8 women; mean age, 58.6 years; range, 41 to 78 years) with severe chronic thromboembolic pulmonary hypertension underwent BPA. We performed a total of 44 BPA in a staged fashion (average 4.4 sessions per patient). We used a plastic jacket guide wire to pass the obstructive lesions of pulmonary arteries, and then replaced with a conventional coil wire by using a micro-catheter. Before balloon expansion, we measured the strict diameter of target vessels by intravascular ultrasound and determined appropriate size of balloon catheters. By those considerations, it was possible to minimize the risk of complications, such as guide wire perforation or rupture of the pulmonary artery, during BPA procedures. All patients received post-procedural management, such as cardiorespiratory monitoring and if necessary, overnight masked positive-airway-pressure ventilation in a cardiac care unit.
Results: As a consequence of BPA, mean pulmonary artery pressure decreased from 52.3±12.5 to 32.7±13.9 mm Hg (P<0.001) and pulmonary vessel resistance decreased from 15.0±5.7 to 7.4±4.9 Wood units (P<0.001). Clinical status of the patients also significantly ameliorated; World Health Organization functional class of the patients improved from 3.1 to 1.5 (P<0.001).
Conclusions: Our results demonstrated that BPA improved pulmonary hemodynamics and clinical status of patients with severe chronic thromboembolic pulmonary hypertension. Careful BPA procedure and post-procedural management should be considered as an effective therapeutic strategy for patients with inoperable chronic thromboembolic pulmonary hypertension.

P5190 | BEDSIDE
Elevated left ventricular filling pressures in chronic thromboembolic pulmonary hypertension

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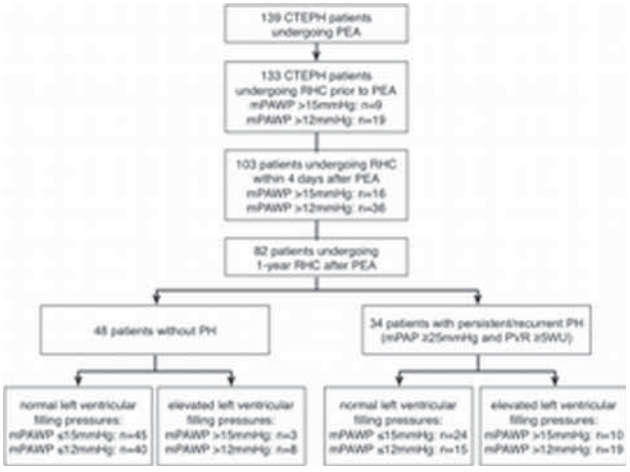
Purpose: Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by non-resolving thromboemboli in the pulmonary arteries. CTEPH is curable by pulmonary endarterectomy (PEA). According to the European CTEPH registry 16.7% of patients experience persistent or recurrent PH after PEA. We hypothesized that a significant proportion of patients with persistent/recurrent PH after PEA carry a post-capillary component.
Methods: 133 consecutive CTEPH patients undergoing PEA were analyzed. Right heart catheterization (RHC) was performed (1) prior to PEA, (2) within 4 days after PEA and (3) after 1 year. Persistent/recurrent PH was defined as mean



CTEPH patient disposition.

pulmonary artery pressure ≥25mmHg and pulmonary vascular resistance ≥5WU 1 year after PEA. Elevated LV filling pressures were defined as (1) mean pulmonary arterial wedge pressure (mPAWP) >15mmHg (PH guidelines), as well as (2)m PAWP >12mmHg (heart failure with preserved ejection fraction guidelines).
Results: Prior to PEA, 9 (6.8%) patients presented with mPAWP >15mmHg and 46 (34.6%) with mPAWP >12mmHg. RHC performed within 4 days after PEA in 103 patients showed that 16 (15.5%) patients had mPAWP >15mmHg while 36 (35%) had mPAWP >12mmHg. Hemodynamic data 1 year after PEA were available in 82 patients. 36 patients were identified as having persistent/recurrent PH. Of those, 10 (29.4%) had mPAWP >15mmHg and 19 (55.9%) had mPAWP >12mmHg. Patients with persistent/recurrent PH and mPAWP >12mmHg were more likely to be male (63% vs. 20%; p=0.012) and to develop atrial fibrillation after PEA (31% vs. 0%; p=0.12) compared to those with mPAWP ≤12mmHg.
Conclusions: CTEPH patients sustain or even increase elevated LV filling pressures immediately postoperative and 1 year after PEA. Increased LV filling pressures seem to play an important role in the persistence or recurrence of PH after PEA.

P5191 | BEDSIDE
External validation of a simple non-invasive algorithm to rule out chronic thromboembolic pulmonary hypertension after acute pulmonary embolism

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Purpose: International guidelines do not provide clear recommendations on medical follow-up after acute pulmonary embolism (PE) including screening programs for chronic thromboembolic pulmonary hypertension (CTEPH). We aimed to externally validate the performance of the non-invasive "CTEPH rule-out criteria" [Thromb Res 2011;128:21-6] to exclude CTEPH in the long-term course of PE based on a normal NT-proBNP level (below age- and gender-adjusted threshold) and the absence of 3 specific ECG characteristics.
Methods: 134 consecutive patients with acute PE underwent echocardiography 6 months after the initial diagnosis. Predefined echocardiographic criteria were used to categorize patients as either "pulmonary hypertension (PH) unlikely" or "PH possible/likely" according to the ESC guideline. The latter patients underwent further (invasive) diagnostic procedures. NT-proBNP, high-sensitive troponin T (hsTnT), and ECGs, all assessed at the day of echocardiography, were evaluated post-hoc.
Results: Sixty-three patients (47%) scored none of the criteria, of whom 61 had a normal echo (97%). Twenty-five patients (19%) were categorized by echo as "PH possible/likely"; of those, 6 were diagnosed with CTEPH. The sensitivity of the CTEPH rule-out criteria to exclude CTEPH was 100%, and to exclude echocardiographic defined "PH possible/likely" 92% (23 of 25 patients identified): 2 asymptomatic patients with elevated estimated systolic pulmonary artery pressures of 36 mmHg and 38 mmHg, respectively, who remained echocardiographically stable during further 2-year follow-up, were not identified. Inter-observer agreement for the adjudication of the ECG characteristics was excellent (kappa-statistic 0.97). The use of hsTnT with a threshold of 14 pg/ml in combination with the ECG criteria instead of NT-proBNP was associated with a sensitivity of 50% to exclude CTEPH (3 of 6 patients identified).
Conclusions: In this external validation cohort, we confirmed the excellent diagnostic accuracy and reproducibility of the CTEPH rule-out criteria. When applied as first test in a CTEPH screening program, echocardiographic examination could have been avoided in half of our patients.

P5192 | BEDSIDE
Phenprocoumon dose requirements and genetic polymorphisms in chronic thromboembolic pulmonary hypertension

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Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by large fibrotic thrombus in the pulmonary arteries, likely originating from pulmonary embolism. Inadequate anticoagulation is one of the suspected mechanisms of disease in CTEPH.
The aim of our study was to assess phenprocoumon dosing in relation to genetic polymorphisms of vitamin K epoxide reductase complex subunit 1 (VKORC 1) and cytochrome P-450 2C9 (CYP2C9).
Patients and methods: The ratio of weekly mean phenprocoumon dose in relation to mean INR levels was assessed in CTEPH patients on phenoprocoumon oral anticoagulation for at least 6 months, compared with PAH patients. VKORC 1 (-1639, -3730) and CYP2C9 (*2, *3) single nucleotide polymorphisms (SNPs) were determined by polymerase chain reaction (PCR).
Results: In 72 patients (46 CTEPH, 26 PAH; mean treatment duration was over 51.7±44.7 months, and mean age was 63.4±12.2 years (63% female). Mean dose of phenprocoumon per week was 15.8 mg (4.5 mg to 42 mg). The mean ratio of weekly phenprocoumon dose and INR levels showed statistically significant differences between CTEPH (mean ratio 6.58±3.3) and PAH (mean ratio 4.87±1.7; P=0.013). Patients with CTEPH and VKORC1 -1639 GG homozygous wild type required significantly higher phenprocoumon doses compared with VKORC1 -1639 AA homozygous mutants (P<0.05). No statistically significant difference was found between the two subsets of CYP2C9 (*2, *3).
Conclusions: CTEPH patients require more phenprocoumon in relation to INR levels than PAH patients. Unmet phenprocoumon dosing requirements may be one mechanism of disease in CTEPH.

P5193 | BEDSIDE
Percutaneous transluminal pulmonary angioplasty ameliorates metabolic and renal dysfunctions associated with hemodynamic improvement in patients with chronic thromboembolic pulmonary hypertension

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Background: Metabolic impairment, such as insulin resistance and dyslipidemia, has been reported to be associated with development of pulmonary hypertension. Recently, we have reported that percutaneous transluminal pulmonary angioplasty (PTPA) markedly improves pulmonary hemodynamics and mid-term prognosis of patients with chronic thromboembolic pulmonary hypertension (CTEPH). In this study, we tested our hypothesis that PTPA is effective to improve metabolic and renal impairments in CTEPH patients.
Methods and results: From March 2012 to May 2013, we examined serum lipids, serum fatty acids fractions, plasma glucose, and immunoreactive insulin in 51 CTEPH patients, and calculated the homeostatic model assessment of insulin resistance (HOMA-IR) using samples from non-diabetic patients. Renal function was assessed by estimation of glomerular filtration rate (eGFR) and urinary albumin/creatinine (U-A/C) ratio. We also evaluated cardiac fatty acid and glucose metabolic state by [123I]-BMIPP SPECT and [18F]-FDG PET. In 27 out of the 51 patients, the measurements were repeated after PTPA. Among the 51 patients, 4 had WHO functional class IV, 7 had 6 minute-walk distance <300m, and 13 had cardiac index (CI) <2.0 l/min/m^2. Enhanced [123I]-BMIPP and [18F]-FDG accumulation in the right ventricular (RV) free wall was noted in 14. The mean value of eicosapentaenoic acid to arachidonic acid (EPA/AA) ratio was 0.42. Regarding glucose metabolism, mean HOMA-IR was 3.6 and insulin resistance (defined as HOMA-IR >2.5) was noted in 22 out of 51 (54%). Regarding renal function, mean eGFR was 63.4±3.0 ml/min/m^2 and U-A/C ratio was 77.1±35.5 mg/gCre. Chronic kidney disease (CKD) in stage 3 or more was noted in 25 patients (49%). We performed PTPA (2±1.6 sessions) in 27 patients (57±15 years, 22 female). PTPA markedly improved pulmonary vascular resistance (-143±45[SD] dynes·sec·cm^{-5}, P=0.001), mean pulmonary arterial pressure (-3.6±1.8 mmHg, P=0.03), mean right atrial pressure (1.6±0.8 mmHg, P=0.03), and heart rate (-3±2/min, P=0.03). [123I]-BMIPP and [18F]-FDG uptake in the RV free wall was also decreased after PTPA. Surprisingly, PTPA significantly improved body mass index (0.46±0.20 kg/m^2, P=0.048), EPA (22.6±7.8 mg/dl, P=0.01) and EPA/AA (0.12±0.04, P=0.02). PTPA also significantly improved eGFR (5.2±1.2 ml/min/m^2, P<0.001) associated with reduction in microabuminuria (-68.5±56.3 mg/gCre, P=0.05).
Conclusions: These results indicate that metabolic and renal dysfunctions are commonly present in CTEPH patients, for which PTPA is highly effective, associated with improvement of pulmonary hemodynamics.

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A gradual improvement without functional restenosis one year after percutaneous transluminal pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

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Aims: Percutaneous transluminal pulmonary angioplasty (PTPA) has been demonstrated to be effective for treatment of chronic thromboembolic pulmonary hypertension (CTEPH). However, the course of improvement and functional restenosis in PTPA has not been clarified yet.
Methods: Among 103 patients with CTEPH (average age: 62±11 years old, male/female: 8/95, the number of PTPA per patient: 3.6±1.6, post-endarterectomy: 6) who underwent PTPA from January the first 2009 to December 31st 2013, 38 completed the follow-up right heart catheterization both at 6 and 12 months after the final PTPA. Hemodynamic parameters including mean pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) at baseline and final PTPA, and at 6 and 12 months after the final PTPA were compared.
Results: PAP and PVR significantly improved in the course (baseline vs. final PTPA vs. 6 months vs. 12 months after the final PTPA; PAP: 42.7±9.8 vs. 27.3±7.9 vs. 21.8±3.3 vs. 19.9±4.0 mmHg; p<0.01; PVR: 10.2±5.1 vs. 5.0±2.8 vs. 3.1±1.3 vs. 2.9±1.6 wood unit; p<0.01, at 6 months vs. 12 months: no significant change).
Conclusions: Hemodynamic parameters improved gradually during course of a year and did not deteriorate one year after the angioplasty, meaning no functional restenosis.

P5195 | BEDSIDE

Short-term impact of balloon pulmonary angioplasty on exercise capacity and ventilatory inefficiency in patients with inoperable chronic thromboembolic pulmonary hypertension

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Purpose: We have previously demonstrated that ventilatory inefficiency improves in the early-phase, while exercise capacity increases continuously toward the late-phase after pulmonary endarterectomy (PEA) in chronic thromboembolic pulmonary hypertension (CTEPH). Recently, balloon pulmonary angioplasty (BPA) has been reported to improve hemodynamics and functional capacity, with an acceptable risk, in patients with CTEPH, who are not candidates for PEA. However, little is known about the detailed, short-term effects of BPA on exercise capacity and ventilatory efficiency in patients with inoperable CTEPH. Thus, the aim of the present study was to determine short-term impact of BPA on exercise capacity and ventilatory efficiency, relative to hemodynamic improvements, in patients with inoperable CTEPH, using cardiopulmonary exercise testing (CPX).
Methods: We enrolled 19 consecutive patients (mean age, 66±9 years; 13 women) with inoperable CTEPH who underwent a series of BPA (3.3±1.5 procedures) between March 2013 and February 2014 and whose recordings of CPX before and after a series of BPA were available. Hemodynamic study and CPX were performed before the first BPA and at a mean of 3.6±4.4 weeks after the final BPA.
Results: At baseline, peak oxygen uptake (peak VO2, 59.7% of predicted) was moderately reduced with the concomitant increase in the ventilatory response to carbon dioxide production (VE-VCO2 slope), reflecting reduced exercise tolerance with impaired ventilatory efficiency in inoperable CTEPH. BPA markedly ameliorated mean pulmonary arterial pressure (mPAP, 35±10 to 23±5 mmHg), cardiac index, mean right atrial pressure, and total pulmonary resistance (863±313 to 466±159 dyne sec/cm5) (all $P<0.01$), without death or major complications including severe reperfusion pulmonary edema. Furthermore, BPA significantly improved World Health Organization functional class, brain natriuretic peptide level (126±166 to 28±11 pg/ml), and 6-minute walk distance (all $P<0.05$). After BPA, peak VO2 (15.2±3.6 to 17.3±2.9 ml/kg/min), VE-VCO2 slope (45±8 to 40±10), peak work load (WR), and $\Delta VO2/\Delta WR$ all significantly improved (all $P<0.05$). Changes in VE-VCO2 slope significantly correlated with those in mPAP ($R=0.46$, $P<0.05$), although the correlation between peak VO2 and mPAP did not reach statistical significance ($R=0.41$, $P=0.08$).
Conclusions: These results suggest that BPA could ameliorate both impaired exercise capacity and ventilatory inefficiency during exercise in short-term, safely by ameliorating hemodynamic abnormalities in patients with inoperable CTEPH.

P5196 | BEDSIDE

Pulmonary endarterectomy in a country without pulmonary endarterectomy: the favorable impact of a cross-border system of care

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Purpose: Pulmonary endarterectomy (PEA) is the treatment of choice for Chronic Thromboembolic Pulmonary Hypertension (CTEPH) and can be curative. PEA is not routinely available in Portugal but the patient is fully reimbursed by the Portuguese National Health Service if surgery is performed abroad. We aimed to assess treatment options and outcomes for patients with CTEPH in a country where there is limited access to PEA, namely if there are any barriers to foreign referral.
Methods: We performed a multicenter, retrospective analysis of 140 patients diagnosed with CTEPH in six pulmonary hypertension centers in Portugal during the last 10 years. Surgical status (operated vs. non-operated) was available for all patients; the remaining clinical and follow-up data was available for 87 patients.
Results: The mean age of CTEPH patients was 57±15 years, with a female preponderance (66%). Surgery was performed in 43 patients (31%), consisting of 42 PEA and 1 heart-lung transplantation due to concomitant severe left ventricular dysfunction. PEA mortality rate was 7.1%. Although patients submitted to PEA were significantly younger (50 +/ 15 vs. 61±12 years, $p<0.001$), their functional capacity as assessed by NYHA class (NYHA class II or IV 84% vs. 69%, $p=0.104$) or 6-minute walking test (366±96 vs. 366±119 m, $p=0.966$) was similar to patients not submitted to PEA. No differences were also found regarding pulmonary vascular resistance (11.6±4.7 WU vs. 10.6±7.3 WU, $p=0.535$). However, 6MWD increased significantly more when patients were submitted to PEA than when treated with pulmonary vasodilators (+110 m vs. 3 m, $p<0.001$). At presentation to the expert center, 23% of patients were already treated with selective pulmonary vasodilators. Half of patients submitted to PEA did not require any pulmonary vasodilator after surgery, whereas 12% required double or triple combination therapy. Almost 75% of patients with CTEPH not submitted to PEA were on pulmonary vasodilators (39% single, 24% double and 9% triple combination therapy), most commonly an endothelin receptor antagonists, followed by sildenafil and prostanoids.
Conclusions: Portuguese patients can access and benefit from PEA through bilateral agreements but are limited by the need of cross-border treatment. Although PEA results are similar in comparison with published registries, CTEPH prevalence might justify a center in our country.

P5197 | BEDSIDE

Chronic thromboembolic pulmonary hypertension after first episode of pulmonary embolism? How often?

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Purpose: Surviving of pulmonary embolism (PE) brings a risk of thromboembolic disease chronicity. Chronic thromboembolic pulmonary hypertension (CTEPH) developes as a result of one or multiple pulmonary embolic event. It is a disabling long-term complication of thomboembolic disease and its importance is not only in a negative impact on patient's quality of life, but especially in recent and emerging treatment possibilities, giving hope even for full recovery. During 2-year follow-up we tried to answer a question of CTEPH incidence in patients surviving pulmonary embolism as the first documented trhomroboembolic event.
Methods: In a study population of 97 consecutive patients with CT-angiographically prooved diagnosis of PE as the first documented thromboembolic event we performed systematic echocargiographic and clinical 2-year follow-up. Echocardiography was performed on admission, at the time of hospital discharge and during 6-, 12- and 24-month visit, with an emphasis on pulmonary artery systolic pressure estimation and right ventricle diameter and systolic function. Symptomatic patients with pulmonary hypertension underwent lung perfusion scan and heart catheterisation to confirm CTEPH.
Results and conclusions: CTEPH was proved in four patients of our study population representing a CTEPH incidence of 4,2%. Our data are consistent with the literature and highlight that the disease deserves taking into consideration and ambulatory medical care of patients after PE must not end with an anticoagulant therapy management.

P5198 | BEDSIDE

RV functional reserve predicts exercise capacity and ventilatory efficiency in patients with chronic thromboembolic pulmonary hypertension

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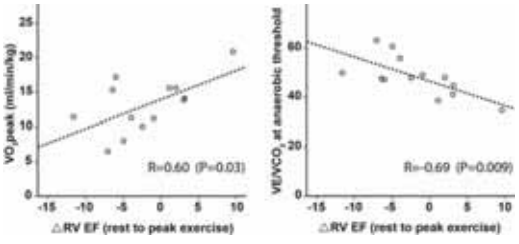
Introduction: Although patients with pulmonary hypertension suffer from exertional dyspnea, hemodynamic assessment is generally performed at rest. We evaluated the left and right ventricular (LV and RV) volume response to exercise and their relation to functional capacity and ventilatory efficiency in patients with chronic thromboembolic pulmonary hypertension (CTEPH).
Methods: Fourteen CTEPH patients underwent cardiopulmonary testing to measure peak-exercise oxygen consumption (VO2peak) and ventilatory equivalent for carbon dioxide (VE/VCO2) at the anaerobic threshold. Subsequently, cardiac magnetic resonance (CMR) imaging was performed at rest and during supine bicycle exercise to near-maximal exertion with simultaneous invasive measurement of mean pulmonary arterial pressure (mPAP).
Results: VO2peak correlated with resting and peak-exercise mPAP ($r=-0.59$ and -0.52, $P<0.05$) and stroke volume index (SVi; both $r=0.59$; $P<0.05$) and with the exercise-induced change in RV ejection fraction (EF; $r=0.60$, $P=0.02$). Similarly, VE/VCO2 correlated with mPAP at rest ($r=0.64$, $P=0.02$), with resting and peak-exercise SVi ($r=-0.58$ and $r=-0.59$, $P<0.05$) and the exercise-induced change in RVEF ($r=-0.69$, $P=0.009$). Both for VO2peak and VE/VCO2, no association was found with resting RVEF. On multivariate analysis, only the exercise-induced change in RVEF, and peak-exercise heart rate and mPAP were independent predictors (standardized beta=0.76, 0.61 and -0.43 respectively, $P<0.05$) and together explained 79% of the variance in VO2peak. For VE/VCO2, the exercise-induced change in RVEF was the only independent predictor (standardized beta =-0.69, $P=0.009$).



Conclusion: In CTEPH patients, exercise measures of RV function and hemodynamics reflect exercise capacity and ventilatory efficiency better than resting measures.

P5199 | BEDSIDE
Usefulness of optical coherence tomography imaging in chronic thromboembolic pulmonary hypertension

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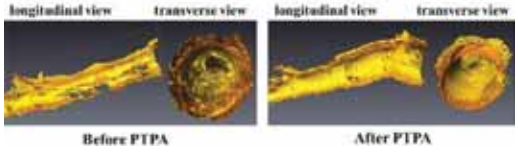
Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by unresolved thromboemboli in the pulmonary arteries (PA). We have previously demonstrated the usefulness of optical coherence tomography (OCT) to diagnose CTEPH, which is an interferometer-based imaging modality with a high resolution. In the present study, in order to develop an effective and safe treatment for inoperable CTEPH, we examined the effectiveness of percutaneous transluminal pulmonary angioplasty (PTPA) combined with OCT evaluation.
Methods: From July 2009 to December 2013, we prospectively enrolled 48 consecutive patients with inoperable CTEPH (41±11 [SD] yrs., 77% females). After optimal medical treatment, we performed PTPA in a step-wise manner until mean pulmonary artery pressure (PAP) reached the level of less than 30 mmHg.
Results: We performed 279 OCT examinations in order to observe the target lesions for PTPA, which clearly showed meshwork (85%), wall thrombus (10%), and slit (5%). We also performed a total of 232 PTPA procedures, which resulted in significant improvement of mean PAP (41.1±10.4 to 25.7±5.4 mmHg, $P<0.001$) and pulmonary vascular resistance (738±345 to 283±97 dyn·sec·cm^{-5}, $P<0.001$) in all patients. OCT showed that PTPA enlarged the lumen diameter (63±90% increase). Furthermore, 3D-OCT imaging more clearly revealed that PTPA destroyed the typical flaps and webs and shifted them to the pulmonary artery walls (Figure). The complication of PTPA was mild to moderate hemoptysis in 16 out of the 48 patients, which was successfully managed with oxygen and non-invasive positive pressure ventilation without intubation.

Figure. 3D-OCT imaging of the target lesion for PTPA



Conclusion: OCT-guided PTPA combined with medical treatment markedly ameliorates pulmonary hemodynamics of patients with inoperable CTEPH.

P5200 | BEDSIDE
The efficacy and safety of the balloon pulmonary angioplasty (BPA) for inoperable chronic thromboembolic pulmonary hypertension (CTEPH) - preliminary results

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Purpose: The purpose of this study was to assess safety and benefits of the BPA procedure. Hemodynamic measures and functional NYHA class, before and after BPA, were compared within the group of patients undergoing BPA (group A). Comparison of outcomes between the group A and the historical control group on targeted PAH therapy (sildenafil, bosentan, treprostinil, riociguat) was also performed.
Methods: From 36 patients (aged 62,2±14,66; 20 females) diagnosed with CTEPH between 2001 and 2013, who were disqualified from pulmonary endarterectomy (PEA) due to distal localization of thrombi, 8 patients (aged 56,5±17,4; 6 females) were found suitable for BPA. The remaining 28 patients (aged 63,85±13,7; 14 females) who received optimal medical therapy for at least 3 months served as control group (group B). The total of 11 BPA procedures were performed in group A. Overall 34 segmental pulmonary arteries have undergone angioplasty. For each patient in group A, a right heart catheterization (RHC) was performed directly before and after each BPA procedure. In group B results from RHC performed at baseline and after at least 3 months of targeted therapy were compared. Baseline and follow-up functional capacity (NYHA class) and hemodynamic measures including pulmonary vascular resistance (PVR), mean pulmonary artery pressure (mPAP), cardiac index (CI), cardiac output (CO) and mean right atrial pressure (mRAP) were recorded.
Results: Comparisons within the group A, before and after BPA, showed significant decrease in PVR (11,00±6,01 vs 10,08±5,65 Wood units; $p<0,032$) and mPAP (52,90±15,19 mm Hg vs 48,18±12,92 mm Hg; $p<0,021$) and improvement of at least one NYHA functional class in group A vs group B (50% pts vs 3,6% pts; p=0,005). No improvement of hemodynamic measures or NYHA class was noticed within the follow-up period for patients from group B. There were no deaths in group undergoing BPA, but several complications occurred including hemoptysis (n=3), dyspnea (n=3), reperfusion pulmonary injury (n=2), desaturation (n=3), atrial arrhythmia (n=1) and subcutaneous hematoma (n=1).
Conclusions: Despite mild complications, in selected CTEPH patients, BPA may offer an additional option for patients not suitable for PEA. It provides early significant improvement of functional NYHA class and reduction of PVR and mPAP. More information on early and long term results are required.

MYOCARDITIS

P5202 | BENCH
The forkhead transcription factor FoxO3a regulates NK cell function - role in CVB3 myocarditis

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Background: FoxO3a is a transcription factor involved in cell metabolism, survival and immunity. For several FoxO3a promoter polymorphisms an association with longevity and differential outcomes in inflammatory disease have recently been reported. However, mechanistic insight in FOXO3a effects is still limited. Here, we investigated the role of FoxO3a on NK cell responses and its effects in pathogen-induced viral myocarditis.
Methods: The effects of FoxO3a viral load and inflammation were investigated a murine model of Coxsackie B3 (CVB3) myocarditis in WT and FoxO3a deficient mice. Foxo3a dependent regulation of CVB3 replication was determined in cell culture in vitro. Functional characterization of NK cells was performed by surface marker expression, cytotoxic assay and IFNgamma expression.
Results: FoxO3a–/– mice were characterized by significantly reduced inflammation, lower viral titers and attenuated expression of pro-inflammatory cytokines in cardiac tissue associated with decreased tissue injury compared to wild-type littermates 7 days post infection. Interestingly, viral titers were attenuated in Foxo3a–/– mice at day 3 while IFNg and NKp46 expression were significantly upregulated in cardiac tissue suggesting early viral control by enhanced innate immune responses. Interestingly, Foxo3a gene transfer in vitro significantly inhibited post-entry CVB3 replication without regulating adhesion or cellular entry. In line with accelerated viral clearance, NKp46+ splenic NK cells of FoxO3a–/– mice exhibited a superior functional status ex vivo determined by enhanced expression of the activation marker CD69, higher frequencies of differentiated CD11b/CD27 effector NK cells and increased cytotoxicity compared to NK cells of WT littermates. Moreover, miRNA-155 expression, recently reported to be essential in NK cell activation and IFNgamma expression, was significantly elevated in FoxO3a–/– NK cells while its inhibition led to diminished production of IFN-γ in FoxO3a–/– mice. In line with our murine data, healthy humans heterozygous or homozygous for the longevity-associated FoxO3a SNPs rs9400239a/rs12212067 exhibited significantly reduced cytotoxic degranulation of NK cells.
Conclusion: Taken together our results implicate FoxO3a in regulation of NK cell activation, differentiation and function and suggest that FoxO3a plays an important role in the innate immune response to viral infection. Thus, enhanced FoxO3a actitvity may be protective for diseases associated with chronic inflammation such as cancer and cardiovascular disease but disadvantageous to control viral infection.

P5203 | BENCH
The role of endothelin in the myocardial inflammation: experimental studies using the endothelin antagonist SB209670

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Background: Myocarditis and subsequent dilated cardiomyopathy are major causes of heart failure in young adults. Experimental autoimmune myocarditis (EAM) is a mouse model of post-infectious myocarditis and inflammatory cardiomyopathy. The pathological role of endothelin (ET) in myocarditis has not been elucidated.
Methods: EAM was induced by immunization of cardiac myosin peptide with complete Freund's adjuvant on days 0 and 7 in BALB/c mice. An ETA/ETB dual receptor antagonist, SB209670, was administered by a continuous infusion from a subcutaneous pump for 2 weeks.
Results: An increase in the heart-to-body weight ratio was observed in SB209670-treated mice compared with vehicle-treated mice. The heart pathology in SB209670-treated mice was remarkable for gross inflammatory infiltration, in contrast to the lesser inflammation in the hearts of vehicle-treated mice. We found that an ET blockade decreased the number of Foxp3+ regulatory T cells in the heart. The ET blockade also inhibited the expression of the suppressor of cytokine signaling 3 that plays a key role in the negative regulation of both Toll-like receptor- and cytokine receptor-mediated signaling. EAM is a CD4+ T cell-mediated disease. CD4+ T cells isolated from SB209670-treated EAM mice produced less IL-10 and more inflammatory cytokines, IL-6 and IL-17, than those isolated from vehicle-treated mice.
Conclusion: The ET receptor antagonist exacerbated autoimmune myocarditis in mice. Our novel findings may suggest that ET plays an important role in the regulation of inflammation in myocarditis.

P5204 | BEDSIDE
Changes in clinical, biochemical and echocardiographic parameters and their correlations with immunohistological features in patients with inflammatory cardiomyopathy

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Background: Patients with inflammatory cardiomyopathy have a variable degree of improvement in clinical and echocardiographic parameters with standard heart failure therapy.
Aim: To correlate changes in clinical, echocardiographic and laboratory parameters with changes in the number of inflammatory cells in endomyocardial biopsy (EMB) samples in 6-month follow-up.
Patients and methods: We evaluated 40 patients with biopsy proven myocarditis and impaired left ventricular function (left ventricle ejection fraction – LVEF <40%) who had ≤12 months heart failure symptoms. Myocarditis was defined as presence of >14 leukocytes/mm^2 and/or >7 T-lymphocytes/mm^2 in baseline EMB. EMB, echocardiography and clinical evaluation were repeated after 6 months of standard heart failure therapy.
Results: LVEF improved from 25±9% to 42±12% ($p<0.001$), left ventricle end-systolic volume (LVESV) and left ventricle end-diastolic volume (LVEDV) decreased from 158±61 to 111±58 ml and from 211±69 to 178±63 ml. NYHA class decreased from 2.6±0.5 to 1.6±0.6; NTproBNP from 2892±3227 ug/ml to 851±1835 ug/ml (all $p<0.001$). In EMB was observed decrease in the number of infiltrating leukocytes (LCA+) from 23±15 cells/mm^2 to 13±8 cells/mm^2 and decrease in the number of infiltrating T lymphocytes (CD3+) from 7±5 cells/mm^2 to 4±3 cells/mm^2 (both $p<0.001$). The decline in the number of infiltrating LCA+ cells significantly correlated with change in LVEF (R = -0.43; p=0.006), LVEDV (R = 0.39; p=0.012), NYHA classification (R = 0.35; p=0.025), NTproBNP (R = 0,33; p=0.045). Decrease in the number of CD3+ cells correlated with the change of systolic and diastolic diameter of left ventricle (R = -0.33; p=0.038 and R = -0.45; p=0.003), and with change in LVEDV (R = -0.43; p=0.006).
Conclusion: Improvements in clinical status, LV function and NTproBNP levels correlate with changes in number of infiltrating inflammatory cells. This observation suggests that contemporary guidelines-based treatment of heart failure is effective therapeutic approach in patiens with biopsy-proven inflammatory cardiomyopathy.
Acknowledgments: This study was supported by a Grant from IGA MH CR NT14087-3/2013.

P5205 | BEDSIDE
Determinants of myocarditis recurrence: single experience in a tertiary center

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Introduction: Myocarditis (MC) is an under-diagnosed inflammatory cardiac disease, frequently with a benign curse, but potentially lethal. Little is known about factors related with its recurrence. Our aim was to assess the incidence and determinants of new episodes of MC in our population.
Methods: We included 72 patients (pts) consecutively admitted from 2007 to 2013. Cardiac magnetic resonance (CMR) was performed during hospitalization for MC diagnosis.
Results: 56 (78%) patients were men, mean age of 33±10years. Acute chest pain was the main inaugural symptom (92%) and fever at admission was detected in 44 (71%). A viral prodrome was frequently (69%). Troponin I elevation was found in all patients (mean peak level of 22±33ng/ml). Mean BNP, C-reactive protein values at admission were 176±336 pg/ml and 79±76 mg/dl, respectively. An abnormal ECG was present in 54 (75%) pts. Moderate to severe left ventricular (LV) systolic dysfunction (ejection fraction <45%) was present at admission in 13 pts (18%). CMR was displayed at 4±2 days after admission and mean LV systolic function was (59±8%), myocardial oedema was present in 58% and late gadolinium enhancement (LGE) in 92%. Mean hospitalization time was 9±5 days. 53 (74%) pts were prescribed on non-steroidal inflammatory drugs (NSAIDs) during 2±1 weeks after discharge. After a mean follow-up of 3±2years no deaths occurred and 8 (14%) pts had the second episode of MC: all of them occurred in the first year (mean 8±3months) of inaugural diagnosis. A normal ECG at diagnosis (100% vs 14%, $p<0.001$), extension of LGE involving 6 or more myocardial segments (100% vs 49%, p=0.042), oedema in T2 weight imaging (100% vs 53%, p=0.034), higher left end-systolic volume at the first episode (49 vs 32 ml, p=0.038; 4.2±0.6 vs 3.3±0.6 l/min/m^2, p=0.034; respectively) were associated with MC recurrence. In multivariate analysis a normal ECG (OR 14, 95%CI 1.91-105.2) and presence of oedema in T2 weight imaging (OR 11.48, 95%CI 1.54-87.98) were independent predictors of MC recurrence.
Conclusions: In our experience 14% of pts with MC had recurrence of the disease, all cases in the first year after the inaugural episode. A normal ECG and oedema in CMR imaging at the first episode were the only independent predictors of recurrence.

P5206 | BEDSIDE
ST segment elevation in acute myocarditis: a new paradigm?

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Background: Acute myocarditis often displays electrocardiographic changes (ECG), yet their significance is not well established. Considering that cardiac magnetic resonance (CMR) can detect the location, extension and type of injury in acute myocarditis, it is possible that its use could contribute a better understanding of the ECG changes observed in this disease.
Purpose: To correlate the observed ECG changes in patients with acute myocarditis with the type and distribution of myocardial lesions as assessed by CMR.
Methods: Prospective observational study of consecutive patients with the diagnosis of acute myocarditis confirmed by CMR. All patients underwent ECG evaluation on admission and repeatedly during hospital stay. The following ECG changes were analysed: T wave inversion, ST segment depression and ST segment elevation. CMR analysis comprised the presence of T2 hyperintensity (edema) and late gadolineum enchancement (necrosis). For topographical analysis using both ECG and CMR changes, the following locations were considered: anterior (anterior wall and anterior septum), lateral (lateral and posterior walls) and inferior (inferior wall and inferior septum). To analyze the association between the topographic location of ECG and CMR changes, we used the Chi-Square test and Fisher's exact test.
Results: 61 patients (54 male, mean age 33.5±11.8 years) were included. T wave inversion was found in 20 patients (33%), ST segment depression in 7 patients (11%) and ST segment elevation in 39 patients (64%). We identified a statisticaly significant association between ST segment elevation location and necrosis location (Fisher's exact test: p=0.023). This association was particularly strong regarding the anterior location (χ^2=6.46 p=0.011). We did not find a statisticaly significant association between ST segment elevation and edema. No association was found between other ECG and CMR changes.
Conclusions: ST segment elevation correlated topographically with necrosis, but not edema, in patients with acute myocarditis. The remaining ECG changes exhibited no topographical correlation with myocardial injury. Considering that myocardial lesions in acute myocarditis is often mesoparietal and/or subepicardial, it is possible that ST segment elevation may translate non-subendocardial myocardial injury, in addition to transmural lesions as seen in ST segment elevation myocardial infarction.

P5207 | BENCH
Peramivir ameliorate murine myocarditis associated with influenza A virus H1N1pdm

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Purpose: Severe influenza sometimes causes myocarditis. We previously reported that fifteen fulminant myocarditis patients associated with influenza A virus H1N1pdm were seen in the 2009/2010 season in Japan. To analyze effects of peramivir, one of neuraminidase inhibitor, on influenza A virus myocarditis, we investigated cardiac function and the pathological roles of cytokines in murine myocarditis associated with influenza A virus H1N1pdm.
Methods: 8-week-old male BALB/c mice were infected intra-nasally with influenza A virus H1N1pdm, and divided into 2 groups: group C; injected with saline, group P: treated with peramivir. Histological study, echocardiogram and quantitative analysis of viral RNA and mRNA of inflammatory cytokines and adhesion-molecules were performed.
Results: There were no significant difference in survival rate (C: 80%, P: 100%) on day 14, and heart/body weight ratio on day 8. LVDd in group P was significantly smaller than group C on day 8. FS of group P (52.2%, p=0.0001) was significantly higher than FS of group C (26.6%) on day 8. Histological study showed localized myocarditis with lymphocyte infiltration, and myocarditis lesions were found in perivascular area or myocarditis was associated with pericarditis. Myocarditis lesions of group P were smaller than group C. Viral replication in heart and lung was suppressed in group P. Expression of mRNA of inflammatory cytokines and adhesion-molecules was suppressed in group P.

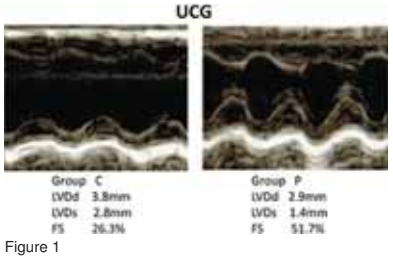

Figure 1

Discussion: Peramivir suppressed viral replication, and also probably improved cardiac function with suppression of cytokines and adhesion-molecules.
Conclusion: Peramivir ameliorate murine myocarditis associated with influenza virus H1N1pdm through suppression of viral replication.

P5208 | BEDSIDE
Etiology of the "idiopathic" arrhythmias and dilated cardiomyopathy: results of myocardial biopsy

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Purpose: Perform a comparative analysis of myocardial biopsy in patients with "idiopathic" arrhythmias and dilated cardiomyopathy (DCM).
Methods: In 74 patients (42 men, 43.6±12,2 years) with "idiopathic" arrhythmias (n=20) and syndrome of DCM (n=54) were performed 46 endomyocardial, 14 intraoperative myocardial biopsy, 5 study of explanted hearts, 9 autopsy with virus investigation (real-time PCR). Among "idiopathic" arrhythmias prevailed atrial fibrillation (n=16). In patients with DCM the average left ventricle diastolic diameter was 6.8±1.1 cm, EF 26.1±11.0%. The control group included 32 patients (16 men, 51.7±12.7 years) with coronary and valvular heart disease, hypertrophic cardiomyopathy, who underwent open-heart surgery.
Results: In group of "idiopathic" arrhythmias myocarditis was detected in 15 patients (75.0%), incl. myocarditis with prevalence of vasculitis (n=4), endocarditis (n=2), and also unverified genetic cardiomyopathy in 3 patients, arrhythmogenic right ventricular dysplasia in 1 and Fabry disease in 1. In group of DCM isolated myocarditis was detected in 33 patients (56.9%), with vasculitis (n=16), endocarditis (n=6), and also association of myocarditis and cardiomyopathy (arrhythmogenic right ventricular dysplasia, myocardial noncompaction, desminopathy) in 10 patients (18.5%) and postinflammatory sclerosis in 2. In DCM also were diagnosed postradiation cardiomyopathy (n=2), amyloidosis (n=1), Emery-Dreifuss dystrophy (n=1) and unverified genetic cardiomyopathy (n=5). In control group myocarditis was found only in 25.0% of patients ($p<0.001$). Morphological marker of patients with arrhythmias was subendocardial lipomatosis (in 65.0%). In DCM degeneration, hypertrophy of cardiomyocytes and focal fibrosis (16.7%) were typical.
Viral genome in the myocardium was detected in 16.7% patients with arrhythmias (parvovirus B19 in 2 cases, herpes virus type 6 in 1), in 55.3% patients with DCM (parvovirus B19 in 16 cases, herpes virus type 6 in 11, cytomegalovirus in 4, Epstein-Barr virus in 7, herpes simplex virus in 5, incl. mixed infection in 10) and in 64.7% patients of control group ($p<0.001$ with group of arrhythmias).
Conclusions: The etiologic structure of "idiopathic" arrhythmias and syndrome of DCM is very similar and represented mainly by myocarditis, different forms of genetic cardiomyopathias and its associations. The frequency of virus detection in the "idiopathic" arrhythmias significantly lower than in DCM and control group. Cytomegalovirus, Epstein-Barr virus and mixed infection were significantly more frequent in DCM.

P5209 | BENCH
CVB3 induces cardiomyocytes apoptosis through regulating HMGB1

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Purpose: The study was to investigate the effects of CVB3-regulated HMGB1 on cardiomyocytes apoptosis.
Methods: Primary cultures of rat cardiomyocytes were cultured and stimulated with CVB3. The expression of bax and bcl-2 was determined. Furthermore,we meausred HMGB1 levels in the supernant, and the expression of intracellular HMGB1 and ace-HMGB1. In addition, the activity of NF-κB and I-κB was also assessed.
Results: 1)The cardiomyocytes, which were stimualted with CVB3 for 36 hours, had significnatly higher levels of bax, bcl-2, and increased ratio of bax to bcl-2 was also detected ($P<0.05$). 2) The intracellular and extracellular HMGB1 levels were markedly raised at 24 and 36 hours after CVB3 ($P<0.05$). Moreover, the cardiomyocytes exposure to CVB3 for 24 hours had significantly higher ace-HMGB1 levels than control ($P<0.01$). Meanwhile, higher ratio of ace-HMGB1 to HMGB1 was also found at 24 hours after CVB3 ($P<0.01$). 3) The expression of p-NF-κB was markedly elevated at 6 hours after CVB3; however, there were no significantly differences of I-κB from 6 hours to 36 hour.
Conclusion: CVB3 induced cardiomyocytes apoptosis through up-regulating ace-HMGB1 levels and increasing intracellular and extracellular HMGB1 expression, which was associated with the activity of NF-κB.

P5210 | BEDSIDE
The diagnostic value of cardiac magnetic resonance in children with acute fulminant myocarditis

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Objectives: To assess the role of cardiac magnetic resonance (CMR) in children with acute fulminant myocarditis (AFM).
Methods: Fifteen patients with AFM aged 3-17 years (AFM group), fourteen patients with dilated cardiomyopathy (DCM) aged 6-14 years (DCM group) and 20 controls aged 3-12 years (Control group) were evaluated from June 2010 to February 2014. All images were acquired using STIR, early gadolinium enhancement (EGE) and late gadolinium enhancement (LGE). Physical examination, plasma cTnT and NT-proBNP, viral PCR in blood, electrocardiogram (ECG) and transthoracic echocardiography were performed in all children.
Results: Typical clinical, ECG and echocardiographic presentations were identified in the AFM group and DCM group. Of fifteen patients with AFM, all had acute heart failure and eight suffered from Adam-Stoke syndrome. Nine patients with AFM underwent CMR within two weeks and the others after one month. Ten of fifteen patients with AFM had LGE imaging. There was significant difference between AFM group (67%) and DCM group (14%) ($P<0.05$). All the controls had normal CMR. Ten of fifteen patients with AFM had abnormal CMR with a sensitivity of 73%, specificity of 100%, positive predictive value of 100% and negative predictive value of 83%, when compared with their clinical findings. Of fifteen patients with AFM, one had abnormal T2WI signals in intraventricular septum (IVS), eight had regional myocardial thinning (including anterior wall, lateral wall, posterior wall and apex of LV and IVS), four had regional myocardial thickening in IVS, four had small pericardial effusions. Using viral PCR in blood, all fifteen patients with AFM had viral infections including Epstein-Barr virus (EBV) (10/15), cytomegalovirus, human herpes virus and adenoviruses. Of the eight patients with regional myocardial thinning by CMR, seven were EBV-positive. In all patients with DCM we found significant dilated cardiac chambers and reduced LV function. The hypersensitive cTnT level in the AFM group were significantly higher than that in the DCM group ($P<0.05$). There was no difference in NT-proBNP level between the AFM group and DCM group ($P>0.05$). Eight of ten patients with ST-T-changes mimicking myocardiac infarction had LGE on the same area of myocardial damage. Six patients underwent CMR during both acute phase and recovery phase, three patients recovered completely and three patients improved.
Conclusions: CMR is a safe and useful technique for diagnosis and follow-up in children with AFM.

P5211 | BENCH
Sphingosine 1-phosphate alleviates Coxsackievirus B3-induced myocarditis by increasing invariant natural killer T cells

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Purpose: Sphingosine 1-phosphate (S1P), via binding to its specific receptors (sphingosine 1-phosphate receptors 1-5, S1PR1-5), participates in the regulation of both innate and adaptive immunity. And recent reports have identified S1P as a second messenger mediating inflammation. However, the roles of S1P in Coxsackievirus B3 (CVB3)-induced myocarditis were unclear. In this study, we investigated the effect of S1P treatment on CVB3-induced myocarditis in vivo.
Methods: BALB/c mice (14-16g) was injected intraperitoneally with CVB3 to establish the viral myocarditis model. Mice were randomly divided into 4 groups. Normal control (Normal) group, S1P control (S1P) group, acute viral myocarditis (Virus) group and S1P treatment (Virus+S1P) group. Myocardial histopathology changes of all groups were observed by H.E stain. Inflammation areas of the myocardium were measured with Image-Pro Plus 6.0. iNKTs in splenocytes and peripheral blood were analyzed by flow cytometry. CVB3 capsid protein VP1 was detected to measure the amount of CVB3 in the myocardial tissue with both western blot and IHC.
Results: The results showed that CVB3 infection downregulated S1PR1 and S1PR5 expression in the myocardial tissue and decreased the proportion of invariant natural killer T cells (iNKTs) in CD3 positive T cells both in spleen and in peripheral blood accompanied by more severe inflammation lesions and more virus capsid protein (VP1) expression in heart tissue. In comparison, S1P treatment resulted in significant S1PR1 and S1PR5 upregulation in heart tissue, upregulation of iNKTs in spleen and peripheral blood, amelioration of myocardial inflammation infiltration and downregulation of myocardial VP1 expression.
Conclusion: These results demonstrated that S1P treatment could alleviate CVB3-induced myocarditis by increasing invariant natural killer T cells.

P5212 | BEDSIDE
Patients with suspicion of myocarditis and normal ejection fraction: role of speckle tracking echocardiography

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Objectives: The aim of this study is to evaluate the diagnostic accuracy of left ventricular (LV) function analysis by speckle tracking echocardiography (STE) in patients with suspected myocarditis and preserved left ventricular ejection fraction (LVEF) and to correlate these parameters with the delayed enhancement (DE) area.
Methods: Nineteen patients with suspected myocarditis and preserved LVEF

were examined; they underwent CMR and echocardiography the same day. In patient with DE we calculated the percentage using the 2 standard deviation (SD) method. A complete echocardiographic examination was performed in all patients. LV function was studied by EF calculated by Simpson's method and by an off-line complete speckle tracking analysis, including LV longitudinal, radial, circumferential strain and LV torsion.
Results: Twelve patients showed DE with non-ischemic pattern. These patients presented a significantly lower apical-radial strain (26.8% vs 32.5%, p<0.0001) and a lower LV apical rotation (6.4 deg vs 7.4 deg, p=0.01) compared to subjects without DE. Among patients with DE we found significant correlations between DE percentage and global LV apical (R -0.77; p=0.0002) and basal (R -0.35; p=0.01) radial strain, LV torsion (R -0.28; p=0.01) and LV apical (R 0.36; p=0.01) and basal (R -0.20; p=0.05) rotation. No significant correlation was found with longitudinal strain and the percentage of DE.
Conclusions: In patients with myocarditis and preserved LVEF, LV apical-radial strain and LV apical rotation correlate with the presence and the percentage of DE.

P5213 | BEDSIDE
A high number of ventricular premature beats (>1000/24 h) predicts adverse events in cardiac sarcoidosis

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Purpose: Cardiac sarcoidosis (CS) has a variable course. Ventricular premature beats (VPBs) are common in CS and we thus examined their role as a predictor of adverse events.
Methods: This study involved 52 patients with histologically verified CS that were managed at our institution over the last 13 years and had at least one 24-hour Holter recording available for analysis. The outcome endpoint was time to the first adverse event of a composite of death, cardiac transplantation, complete atrioventricular block, ventricular tachycardia (requiring treatment) and congestive heart failure.
Results: The patients were aged on average 48 years (SD 9.87) and 73% of them were females. Left ventricular ejection fraction at presentation averaged 54% (range, 23% to 85%). The mean duration of follow-up after diagnosis was 32 months (range, 0 to 83 months). The highest number of VPBs in a 24-hour Holter at diagnosis was <1000 in 16 patients (31%), 1000-10.000 in 22 patients (42%) and >10.000 in 14 patients (27%). An adverse outcome event occurred in 1/16 patients with <1000 VBPs, in 11/22 patients with 1000-10.000 VPBs and in 11/14 patients with >10.000 VPBs (Log-Rank p=0.009). The Kaplan-Mayer estimates for mean survival free of an adverse events was 67 months, 52 months and 34 months in the groups with <1000, 1000-10.000 and >10.000 VPBs per 24 hours, respectively. In multivariate analysis using Cox regression, the number of VPBs >1000 per 24 hours was predictive of adverse events (p=0.013) along with initial ejection fraction <50% (p=0.059).
Conclusions: Multiple VPBs predict future adverse cardiac events in patients with CS.

PERICARDIAL AND MYOCARDIAL DISEASES

P5215 | BEDSIDE
In cardiac ATTR amyloidosis the extent of myocardial toxicity of amyloid deposits is highly dependent on the specific transthyretin mutation

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Background: When comparing cardiac amyloidoses, it is well known that the prevalence of some findings such as low peripheral ECG voltages or the extent of serum cardiac biomarker increase is quite different, cardiac AL being characterized by a higher prevalence of low voltages and a much more marked elevation in serum NT-proBNP levels, despite a remarkably similar echocardiographic (or MRI) presentation. Also prognosis is different, being worse in cardiac AL that ATTR amyloidosis.
Objective and methods: To compare NT-proBNP release and systo-diastolic function in different etiologies of cardiac amyloidosis, 173 cardiac AL and 102 cardiac m-ATTR patients were evaluated at diagnosis, after excluding patients with renal dysfunction (MDRD-estimated glomerular filtration rate <60 mg/dl).
Results: Despite lower left ventricular mass (LVM, an index of the extent of cardiac amyloid deposition) [174 (138-195) vs. 196 (156-145) g/m^2, median (IQ range), p<0.001], cardiac AL was characterised by a 6-fold higher serum NT-proBNP level [5931 (2330-11957) vs. 994 (564-2328) pg/ml, p<0.001], associated with a more severe extent of diastolic dysfunction [(E/E' ratio: 10.1 (6.7-13.7) vs. 8.4 (6.0-11.2), p<0.02] and comparable systolic function and global longitudinal strain. When subdividing cardiac m-ATTR patients according to the different genotypes, serum NT-proBNP levels were remarkably different among the 23 observed TTR mutations. When compared with LVM-matched cardiac AL patients, Ile68Leu and Val122Ile patients (n=13 and n=6, respectively) had superimposable NTproBNP levels [4795 (1821-8889) pg/ml, p=ns vs. AL] associated with a comparable extent of systolic and diastolic dysfunction. In contrast, NT-proBNP levels were remarkably lower in Val30Met and Glu89Gln (n=28 and n=20) patients ([718 (446-1287) pg/ml, p<0.01 vs. AL]), who had lower E/E' ratio, and higher longitudinal systolic shortening and global strain, compatible with a much more preserved systolic and diastolic function.
Conclusions: In cardiac m-ATTR, the extent of NT-proBNP release is critically dependent on the TTR-related amyloid type, Ile68Leu and Val122Ile being remarkably more toxic than Val30Met and Glu89Gln mutations at comparable extent of amyloid deposition.

P5216 | BEDSIDE
NT-proBNP: an important prognostic marker in familial amyloid polyneuropathy

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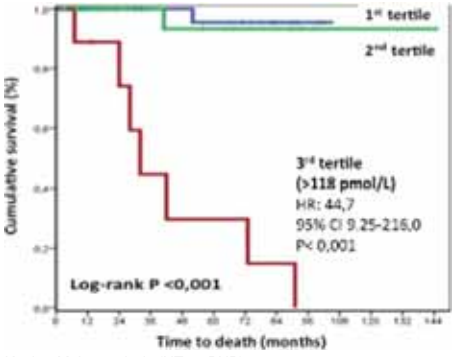
Purpose: Cardiac involvement in familial amyloid polyneuropathy (FAP) V30M-TTR is characterized by progressive myocardial amyloid infiltration, but heart failure is rare, even in advanced forms of the disease. NT-proBNP is a biomarker of cardiac dysfunction and a strong prognostic predictor in other forms of systemic amyloidosis. However its prognostic value in FAP is not well known. The aim of this study is to examine the prognostic value of NT-proBNP in FAP V30M-TTR.
Methods: Prospective observational study of V30M-TTR patients who underwent annual clinical evaluation and periodic serum NT-proBNP measurements. The prognostic value of NT-proBNP was evaluated by multivariate Cox logistic regression analysis (adjusted for age) and Kaplan-Meier survival analysis. Given the non-parametric distribution of NT-proBNP, its logarithmic transformation was used in survival models.
Results: We studied 155 (45±15 years, 56.8% female) FAP V30M-TTR patients. During a median follow-up of 27 months, 374 periodic determinations of serum NT-proBNP were conducted. The median serum level of NT-proBNP was 84 (42-157) pmol/L and increased progressively with age (R: 0.37; P<0.001; Rho: 0.30; P<0.001) and the duration of symptoms (R: 0.18; P=0.017;Rho: 0.22; P=0. 004). The risk of death progressively increased with NT-proBNP concentration [hazard ratio (HR): 4.43, 95% CI 1.22-16.06, P=0.024]. Thus, patients in the 3rd tertile distribution of NT-proBNP (>118 pmol/L) had a significant increased risk of death (HR: 44.7, 95% CI 9.25-216.0, P<0.001).



Kaplan-Meier analysis (NT-proBNP).

Conclusion: Despite the fact that the levels of NT-proBNP are substantially lower in FAP V30M-TTR than in other forms of amyloidosis, this biomarker is still an important predictor of mortality and should be integrated in the evaluation and follow-up of these patients.

P5217 | BEDSIDE
Elevated pulmonary artery systolic pressure predicts poorer survival in constrictive pericarditis

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Purpose: Pulmonary artery systolic pressure (PASP) of more than 50 mmHg is considered atypical of constrictive pericarditis (CP). We investigated the prevalence and correlates of elevated PASP in CP and its impact on survival.
Methods: We reviewed 417 patients with a surgically confirmed diagnosis of CP from January 1985 to October 2006, who underwent preoperative evaluation of PASP by transthoracic echocardiography, cardiac catheterization, or both. Patients were categorized into those with PASP ≥50 mmHg by at least one test (Group II; n=139) and those without (Group I; n=278).

Results: PASP ≥50 mmHg was present in 33% of patients. Group II patients were more often female (odds ratio [OR] 2.29, p=0.002) and more likely to have systemic hypertension (OR 1.69, p=0.035), pulmonary disease (OR 2.23, p=0.005), prior cardiovascular surgery (OR 2.17, p=0.002), significant mitral regurgitation (OR 2.80, p=0.003) or tricuspid regurgitation (OR 2.71, p<0.001). Perioperative mortality (within 30 days of surgery) was 3% and 14% in Groups I and II respectively (p<0.001). Overall survival was poorer in Group II (p<0.001 by log-rank test) (Fig. 1).

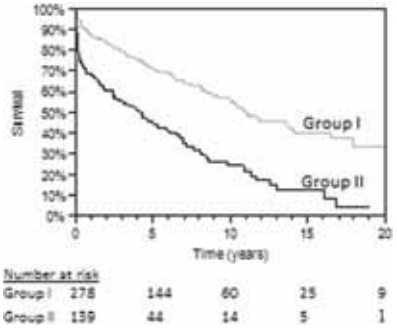

Figure 1

Conclusion: PASP is elevated beyond 50 mmHg in a third of patients with CP. Patients with elevated PASP have poorer perioperative and long-term survival.

P5218 | BEDSIDE
Matrix metalloprotease activity in patients with cardiac AL amyloidosis and in human cardiac fibroblasts exposed to cardiotoxic amyloidogenic light chains

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Introduction: Cardiac fibroblasts represent the majority of cardiac cells within the myocardial wall. Among the many factors that modulate extracellular matrix (ECM) homeostasis, matrix metalloproteinases (MMPs) and MMP specific inhibitors (TIMPs) play an important role. In cardiac AL amyloidosis, amyloid fibril deposition has been shown to result in disruption of myocardial ECM.
Aim: To measure serum MMP and TIMP concentration in cardiac AL patients and to test the hypothesis that light chain (LC) - induced cardiotoxicity is associated with changes in fibroblast-derived MMP activity.
Methods: Serum MMP-2, MMP-9, TIMP-1 and TIMP-2 (ELISA) and MMP-2/MMP-9 gelatinolytic activity (zymography) were assessed in 31 consecutive untreated AL patients with predominant cardiac involvement and in 18 MGUS patients (as a control group). In a parallel experiment, primary fibroblast cell cultures (HCF) derived from normal human myocardial explants were grown in DMEM serum, supplemented with 10% FCS. After seeding ($5x10^2$ cells/cm^2), cells were grown to confluence. Medium was then removed and fresh DMEM containing cardiotoxic LCs (obtained from 3 cardiac AL patients) or LCs derived from 3 MGUS patients (MG-LCs) (100 mg/ml for both) was added for 24 hours.
Results: When compared with MGUS, cardiac AL was associated with higher serum MMP2 (142.2±16.7 vs. 121.9±28.7), MMP9 (16.8±3.35 vs. 3.5±0.89), TIMP-1 (39.5±22.2 vs. 27.8±15.6) and TIMP-2 (24.4±7.5 vs. 20.7±11.9) concentrations (ng/ml/mg protein; p<0.05 for all comparisons). In HCF, incubation with cardiotoxic LCs was associated with significantly higher MMP-2 and MMP-9 activities, when compared with MG-LCs (5.27±0.70 vs. 3.91±0.25, and 4.77±0.61 vs. 3.93±0.23 OD mm^2/mg/ml protein, p<0.05 for both).
Conclusions: Cardiac AL patients show an increased and sustained stimulus to ECM degradation. Exposure to cardiotoxic amyloidogenic light chains increases cardiac fibroblast-derived MMP activity. In vivo, this may cause extracellular matrix degradation, further contributing to the development and maintenance of amyloid-induced cardiac damage.

P5219 | BEDSIDE
Minimally Invasive Strategy For Resection Of Primary Cardiac Tumors: The Leipzig Experience

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Objectives: Here we report our single center experience using the minimally invasive right-sided thoracotomy approach (MIC) in resecting intracardiac tumors.
Methods: Between 1994 and 2010, 252 patients underwent evaluation and treatment of primary cardiac tumors at our institution. Of these, 108 patients underwent minimally invasive surgery through a right mini-anterolateral thoracotomy. The follow-up was 95% complete with a mean follow-up of 10±5 years.
Results: Seventy four patients (68.5%) were diagnosed with myxomas (mean age 65±13 years). In-hospital mortality (HM) was 1.3% (n=1) and was due to non-cardiac causes. Late mortality was 6.8% (n=5). Postoperative morbidity in the form of reoperation for bleeding, arrhythmia and pericardial effusion was 10.8% (n=8), 14.8% (n=11) and 9.5% (n=6) respectively. No recurrent tumors have been diagnosed at follow-up. None of the 31 patients (28.7%) diagnosed as benign non-myxomas (mean age 63±16 years) died after surgery. However, one patient (3.2%) died within four years due to non-cardiac causes. Six patients (19.3%) required reoperation for bleeding, 5 (16.1%) developed arrhythmias and 3 (9.6%) developed pericardial effusion. Of the 3 patients diagnosed with a malignant tumors (mean age 63±16), one patient died within 30 days after surgery. The other two patients required a reoperation at 8 and 14 months after the primary operation because of aggressive tumor recurrence. Within our entire cohort of 108 patients, no patient required conversion from right antero-lateral mini-thoracotomy to sternotomy.
Conclusion: Surgical resection, when possible, is the treatment of choice for all primary cardiac tumors. Minimally invasive surgical approach can be routinely applied with excellent surgical results. However, the entity of tumor formation affects the long-term prognosis.

P5220 | BEDSIDE
Colchicine for the prevention of pericarditis: systematic review and meta-analysis

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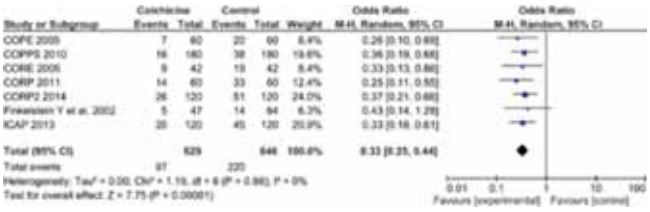
Aims: The purpose of this study was to investigate and summarize available evidence on the efficacy and safety of colchicine for pericarditis prevention. Disease recurrence is the major and most common complication of pericarditis and its prevention may reduce morbidity and management costs. Colchicine has been intensively studied in the last decade for pericarditis prevention.
Methods: Controlled clinical studies were searched in several databases and were included provided they focused on the pharmacologic primary or secondary prevention of pericarditis. We performed a meta-analysis including studies primary outcome, adverse events, and drug withdrawal.
Results: From the initial sample of 175 citations, 7 controlled clinical trials were finally included (1275 patients): 5 studies were double-blind randomised controlled trials (RCT), and 2 studies were open-label RCTs. Trials followed patients for a mean of 19 months. Meta-analytic pooling showed that colchicine use was associated with a reduced risk of pericarditis during follow-up (OR= 0.33 [0.25-0.44], p for effect<0.001, p for heterogeneity= 0.98, I2=0%) either for primary or secondary prevention without a significant higher risk of adverse events compared with placebo (OR= 1.28 95% CI 0.84-1.93), but more cases of drug withdrawals (OR= 1.64 95% CI 1.04-2.58). Gastrointestinal intolerance is the most frequent side effect (mean incidence 8%), but no severe adverse events were recorded.



Forest plot for the risk of pericarditis.

Conclusions: Colchicine is safe and efficacious for the primary and secondary prevention of pericarditis. Gastrointestinal intolerance is responsible for an increased risk of drug withdrawal, mainly due to diarrhoea.

P5221 | BEDSIDE
Survival after alcohol septal ablation in hypertrophic obstructive cardiomyopathy: results from a consecutive patient cohort

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Alcohol septal ablation (PTSMA) is an effective treatment for hypertrophic obstructive cardiomyopathy, however the long-term effects still remain a matter of anxiety. We examined survival of consecutive patients (pts) treated in a referral center.
We followed 111 consecutive pts (53±15 years; 59% men) who underwent septal ablation at our institution between 2005 and 2006. Only 1 target septal branch was occluded in each PTSMA attempt regardless of immediate haemodynamic result. Follow-up was at 3 months after PTSMA and at yearly intervals thereafter. 67 (60%) pts had concomitant hypertension, 13 (12%) had coronary artery disease and 15 (14%) had atrial fibrillation. 17 (15%) pts had a device (7 pacemaker, 10 ICD) implanted before first PTSMA while 12/94 (13%) and 13/94 (14%) received a pacemaker or an ICD after PTSMA respectively. All ICDs were implanted

for primary prevention of sudden death based on risk stratification. 3 (3%) pts had unsuccessful myectomy before PTSMA, 3 (3%) had myectomy at follow-up because of technically futile (no suitable septal branch after contrast echocardiography testing) or partially effective PTSMA, while 1 pt had myectomy both before (unsuccessful) and after (successful) inadequate haemodynamic effect of PTSMA. 18 (16%) had a PTSMA before and 19 (17%) underwent a 2nd PTSMA after the index procedure. 90 (81%) had procedural success with at least 80% gradient reduction without complications. 99 (89%) were treated for pure subaortic, 4 (4%) for midventricular and 8 (7%) for combined subaortic and midventricular obstruction. The intraventricular gradient before first treatment was significantly reduced at last follow-up from 66±39 mmHg to 14±17 mmHg at rest ($p<0,00001$) and from 108±50 mmHg to 26±29 mmHg after Valsalva ($p<0,00001$). Over a follow-up of 5.2±3.2 years after first PTSMA, survival free of all mortality was 95%. In total, there were 5 deaths: 3 of possible cardiac cause (1 sudden death of a 36-year-old male 20 months after 2nd PTSMA, 2 of unknown cause: 67-year-old female 45 months after PTSMA and 78-year-old female 74 months after PTSMA) and 2 noncardiac (69-year-old female with sepsis, 67-year-old female with cancer). For the endpoint of documented sudden cardiac death or unknown cause of death, the incidence per 100 person-year follow-up was 0.5.
PTSMA in an unselected patient cohort treated in a referral center is associated with favourable long-term survival without increased risk of sudden cardiac death. The need for repeated procedures is probably related to our conservative wait-and-see approach with occlusion of only one septal branch at every attempt.

P5222 | BEDSIDE
Feasibility of multimodality treatment for cardiac sarcomas

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Background: Cardiac sarcomas (CS) have a dismal prognosis. Multimodality treatment (MMT) with surgery, radiation (RT) +/– chemo (CT) therapy improves event-free survival of soft tissue sarcomas, but cardiac RT is considered at high risk. Modern RT techniques as Intensity Modulated RT (IMRT) and Tomotherapy (TOMO) concentrate radiation to the tumor volume with limited involvement of surrounding structures.
Purpose: We report our experience with MMT (using IMRT/TOMO) in 22 patients (pts) (14 males, 8 females, aged 22-72, median 44) with 17 high-grade, 5 low-intermediated grade CS (five with local relapse after surgery) seen at our Institutes over 20 years.
Methods: The therapeutic approach was: a) anthracycline CT and/or IMRT/TOMO in resected CS with margin infiltration; b) CT + RT in unresectable CS, followed by surgery if feasible after mass reduction. RT was used in 15 pts, CT in 19. Cardiac evaluation and echocardiograms were obtained before and every 3 months during CT, before and weekly during RT, every 3 months after ending therapy for 2 years, and then yearly.
Results: Out of 22 pts, 13 are dead (1 of pulmonary embolism; 12 of metastases), 2 had metastases at last follow-up (at 15 and 20 months) and have been lost thereafter, 7 are alive 10 to 138 months after starting treatment (of which 5 free of tumor, 2 still on treatment). Early toxicity during CT/RT were paroxysmal atrial fibrillation (AF) in 3 pts (reverted by amiodarone), acute pericarditis in 1. Late toxicity were: localized hypokinesia with globally normal ejection fraction (EF) in 2 pts, mild EF reduction in 2, recurrent AF in 2, and constrictive pericardits in one.

Type of treatments and outcome

Treatment	Total	Dead/lost	Alive	Free of tumor	Survival (months)
Preoperative CT/RT + surgery	2	2			10,12
Surgery + postoperative CT/RT	12	4	5	4	2–61 (mean 23, median 18)
Surgery + pre/postoperative CT and RT	1		1	1	48
CT + RT	4	3	1	1	12–138 (mean 54, median 34)
CT (no surgery)	3	3			9, 6, 6

Conclusions: A patient-tailored MMT including CT and/or RT was safe, with good local disease control. Five out 22 (23%)patients are currently alive, free of disease, at a median of 25 month follow-up and without significant late cardiac adverse effects.

P5223 | BEDSIDE
How are patients with acute pericarditis managed in the emergency room? A real-life study

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Purpose: Most published series of pericarditis are issued from patients treated in cardiology departments, but data on their management in emergency departments (ED) are scarce. We aimed to describe the characteristics and outcomes of patients diagnosed for acute pericarditis (AP) in our ED within a tertiary care university hospital and to compare the management to the 2004 ESC guidelines (2004-GL).
Methods: We retrospectively retrieved all the patients diagnosed for acute pericarditis in our ED from 01/2011 to 06/2013. Data were collected from medical files and through a questionnaire sent to the referring physician to assess the outcome.
Results: During the study period we identified 150 patients (age 41.5±16.2 years, 66% males) of whom 42.5% consulted within the first 6 hours after the symptoms onset, mainly chest pain in 99.3% of cases. The 2004-GL criteria for the diagnosis of AP were met only in 47.6% of cases. An increased (>5mg/l) C-reactive protein (CRP) was present in 51.3% of patients. CRP levels were significantly higher in patients meeting the diagnostic criteria when symptoms were present since >24 hours (79.1 vs. 14.9 mg/l in patient with- vs. without ESC diagnostic criteria, $p<0.029$). In 49% of cases, ECG was compatible with the diagnosis of AP. An echocardiography was performed during the stay in ED in 77.3% of patients, showing a pericardial effusion in 26% of cases. Patients were hospitalized in 27.3% of cases. Aspirin was the most often prescribed (84%). Eleven different therapeutic regimens were encountered. Colchicine alone or in association with aspirin was proposed in 30% of patients and was significantly associated with a medical history of pericarditis (63% with- vs. 25% without history of AP, $p<0.0001$). The duration of drug therapy was longer for colchicine than for other anti-inflammatory drugs (respectively 58±31 vs. 26±13 days, $p<0.01$). Follow-up data were available only for 50 patients: only 52% have consulted their physician within a period of 1 to 120 days after discharge. Treatment side effects were noted in 6% of cases and recurrence in 4% of cases.
Conclusions: Our results highlight the lack of a systematic guidelines-based management of patients with acute pericarditis in the emergency room. The assessment of CRP is of diagnostic value in this setting especially after 24 hours of symptoms onset. This marker may be considered in the future guidelines updates. Since a majority of these cases are managed as outpatients, emphasis should also be made for an adequate and systematic follow-up.

P5224 | BEDSIDE
Recurrence of carcinoid heart disease after surgical valve replacement: a new therapeutic dilemma due to improved perioperative outcomes and survival

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Background: Carcinoid tumors are neuroendocrine malignancies that secrete bioactive substances into the systemic circulation triggering carcinoid syndrome and cardiac involvement. Cardiac manifestations include right-sided endocardial fibrosis and valve dysfunction. Valve replacement is the only definitive treatment. Although surgical mortality has been reported around 20%, superior outcomes together with more effective oncologic therapies have extended overall survival. We sought to determine the incidence and risk factors for recurrence as well as to characterize feasibility and outcomes of reintervention.
Methods: From 1/2001 to 11/2013, 27 patients (30% female; mean age 62±9 years) underwent valve surgery for carcinoid heart disease (CHD). Twenty-two patients (82%) presented isolated right-sided valve disease whereas 5 (18%) had concomitant left-sided disease. A PFO was identified in 4 patients (15%). Biological prostheses were used in those valves requiring surgical replacement. Thirty-day mortality was 11%. Causes of death were right ventricular (RV) failure (n=2) and refractory vasoplegia. Clinical, laboratory and echocardiographic follow-up data was prospectively collected among survivors.
Results: Of the 24 survivors, 11 (46%) had a degree of recurrence on follow-up echocardiography (≥moderate prosthetic dysfunction associated to leaflet thickening absent on discharge). Median time to recurrence was 16 months (IQR11-25). Four patients (36%) were NYHA class ≥III. Median peak levels of serotonin, Chromogranin A, and urinary 5-HIAA were 920ng/ml (IQR608-2328), 2527ng (IQR138-4400), and 159mg/L (IQR16-732) respectively. Median peak levels of Chromogranin A were found to be a significant marker for recurrence (2339.4ng vs. 485.6ng, p=0.004). Echocardiographic analysis revealed > moderate prosthetic dysfunction in 5 (21%) patients of which 4 (16%) had moderate to severe RV dysfunction. Among these, 2 patients underwent reoperative surgery with mechanical valves, 2 received percutaneous balloon valvuloplasty, and 1 was deemed inoperable due to severe tumor burden. Reintervention was successful in all patients.
Conclusion: Recurrence of CHD might be high despite maximized antitumor therapy and is expected to increase due to improved survival. Reintervention in the absence of a near demise is feasible and has excellent outcomes. However, a multidisciplinary approach is mandatory to proceed with appropriate decision making and prosthesis selection. Novel therapies such as tryptophan hydroxylase inhibitors might potentially play a key role in a near future to control tumor activity and avoid recurrent CHD.

P5225 | BEDSIDE
Evaluation of cardiac autonomic functions in patients with myocardial bridge via heart rate recovery

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Purpose: Heart rate recovery (HRR), defined as the rate of decline in the heart rate immediately following the cessation of exercise, is influenced by autonomic function. The myocardial bridge (MB) is an anomaly characterized by a typical intramyocardial route of a segment of one of the major coronary arteries. The aim of the present study was to assess HRR in patients with MB.
Methods: A total of 87 patients with MB were selected from our medical records between January 2012 to December 2013. All patients with MB had a positive exercise stress test. Presence of MB detected by coronary computed tomography angiography in all patients. We compared the clinical and exercise test data of these patients with 73 volunteers matched for age and sex. All exercise stress tests were treadmill stress tests using the Bruce protocol and were symptom limited or pushed to 90% of maximal heart rate in the absence of symptoms. HRR indices were calculated by subtracting first, second, and third minute heart rates from the maximal heart rate obtained during stress testing and designated as HRR1, HRR2, and HRR3.
Results: Patients with MB and control group were similar with respect to age (32.1±8.5 vs. 32.0±9.7 years) and left ventricular ejection fraction (62.0±3.0% vs. 62.7±3.1%). Mean HRR1 (29.6±11.6 vs 35.8±10.4, P=0.001) and HRR2 values (52.7±13.5 vs. 60.0±13.2, P=0.040) were significantly lower in patients with MB than the control group. In addition, HRR1 was more lower in patients with left anterior descending (LAD) coronary artery MB than patients with non-LAD coronary artery MB (28.2±12.1 vs 34.1±8.7, P=0.045).
Conclusions: Patients with MB has lower HRR indices with respect to normal subjects. The HRR index is more impaired in patients with LAD coronary artery MB. These findings are implying the presence of cardiac autonomic dysfunction in patients with MB, especially in LAD involvement.

P5226 | BEDSIDE
Diagnostic accuracy of quantitative PCR (xpert MTB/RIF) for tuberculous pericarditis compared to adenosine deaminase and unstimulated interferon-gamma in a high burden setting: a prospective study

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Purpose: Current tools for rapid, accurate diagnosis of tuberculous pericarditis (TBP) are sub-optimal.
Methods: We evaluated the diagnostic utility of the Xpert-MTB/RIF assay, unstimulated interferon-gamma (uIFNγ), and adenosine-deaminase (ADA) using pericardial fluid (PF) from 151 suspected TBP patients. Mycobacterium tuberculosis culture and/or pericardial histology served as the reference standard. Receiver-operating-characteristic curve analysis was used for selection of uIFNγ and ADA cut-points.
Results: 49% (74/151) of patients were classified as definite-TB, 33% (50/151) as probable-TB (clinical or biochemical diagnosis, reference negative), and 18% (27/151) as non-TB (confirmed alternative diagnosis). Sensitivity, specificity, positive (LR+) and negative (LR-) likelihood ratios (95%CI) were:(i) Xpert-MTB/RIF: 63.8% (52.4-75.1), 100% (85.6-100), >100, 0.49 (0.47-0.51); (ii) uIFNγ (cut-point 44pg/ml): 95.7% (88.1-98.5), 96.3% (81.7-99.3), 25.8 (3.6-183.4), 0.05 (0.02-0.09); (iii) ADA (cut-point 35 IU/l): 95.7% (88.1-98.5), 84% (65.4-93.6), 6.0 (3.7-9.8), 0.05 (0.03-0.1). At 30% TBP prevalence, the specificity and positive-predictive-value (PPV) of uIFNγ was higher than ADA (p=0.03), while the sensitivity and negative-predictive-value (NPV) of uIFNγ and ADA were higher than Xpert-MT/RIF (p<0.001).
Conclusion: Although Xpert-MTB/RIF had excellent PPV, it detected only two thirds of TBP cases. By contrast, uIFNγ detected almost all the TBP cases and offered better rule-in and rule-out value. uIFNγ offers superior accuracy for the diagnosis of microbiologically proven TBP compared to Xpert MTB/RIF and ADA assays.

CARDIOMYOPATHIES – I

P5228 | BEDSIDE
Postmortem genetic testing in a series of 36 young patients after sudden cardiac death

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The incidence of sudden cardiac death (SCD) increases with age in parallel with coronary's diseases' prevalence. In young persons and athletes, SCD occurs in half of the cases, in the setting of genetically transmitted disorders such as cardiomyopathies. Molecular testing performed after necropsy may help management of families but experience in this area appears very limited. The aim is to report our experience of post mortem molecular testing after SCD and necropsy.
We studied 36 patients <40 years who died suddenly with a suspected diagnosis of cardiomyopathy, established either after autopsy or known before death, with 6 dilated cardiomyopathy (DCM), 12 hypertrophic (HCM), 2 HCM/DCM, 1 restrictive (CMR), 14 arrhythmogenic right ventricular cardiomyopathy (ARVC), 1 HMC and left ventricular noncompaction. Sanger sequencing was performed in most 4-5 frequent genes for a given phenotype. Fifteen mutations have been identified in sarcomeric (11 mutations) or desmosomal (3 mutations) or lamin A/C (1 mutation) genes.
The identification of these mutations had significant impact: assessing right diagnosis in a doubtful case (HCM without LVH), modifying the appropriate diagnosis in another case (HCM and not DCM), confirming a genetic disease even in the absence of affected relatives in the family, providing guidance for genetic counselling and predictive genetic testing in relatives in all situations. Technical, ethical and legal issues may however be encountered and will be discussed.
This study is one of rare series of post-mortem molecular testing after SCD. Our findings suggest the feasibility, molecular efficiency and the clinical benefit of the approach in order to improve the management of families. Postmortem molecular testing must take its place in the strategy of family care after SCD, even if a cardiomyopathy is suspected at necropsy, since genetic findings provide additional information useful for the relatives.

P5229 | BEDSIDE
Arrhythmogenic right ventricular cardiomyopathy (ARVC): genetic profile and arrhythmiogenicity

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Purpose: ARVC is mainly a disease of the desmosomes, although there are also other non-desmosomal types of the disease. We investigated the correlation between arrhythmic profile and the presence of a desmosomal mutation (DsM) in our cohort of ARVC patients (pts).
Methods: Thirty-six consecutive ARVC-pts (26 males, 72.2%) were prospectively evaluated and divided into two groups (I&II) based on the identification of a pathogenic DsM. Analyzed genes were Plakophilin, Desmoplakin, Desmoglein, Desmocollin and Plakoglobin. During a 106.7±64.9 months f/u, SCD, history of aborted SCD, appropriate implantable cardioverter-defibrillator (ICD) activation and syncopal episodes were considered as malignant arrhythmic events. Antiarrhythmic medication did not differ between the two groups (amiodarone, sotalol).
Results: Pathogenic DsMs were found in 26/36 pts (72.2%) diagnosed with ARVC (group I). No DsM were identified in the 10/36 (27.8%) pts (group II). Mean age at diagnosis was similar between the two groups (38.0±20.0 group I vs. 33.7±14.2 group II, P=0.543). Group I had a mean f/u of 90.7±49.3 months, whereas group II pts were followed-up for 148.2±83.5 months (P=0.015). In 8 out of 18 mutation-positive families (44.4%) the disease was familial with at least another affected member, whereas in none of mutation-negative families there was evidence of affected relatives (P=0.025). During f/u malignant arrhythmic events occurred more often in group I pts as compared with those of group II (76.9% versus 40%, P=0.045) despite the fact that group II had longer f/u period (Table 1).

Table 1. Major arrhythmic events during follow-up

	Group I (n=26)	Group II (n=10)	P-value
Malignant arrhythmic profile	20/26 (76.9%)	4/10 (40%)	0.045
1. SCD	4	1	0.571
2. Aborted Sudden Death	1	1	0.484
3. Appropriate ICD activation	6	0	0.157
4. Clinical sustained VT with syncope	9	2	0.023

SCD: sudden cardiac death; VT: ventricular tachycardia.

Conclusions: During a long-term f/u, ARVC pts with DsMs had a higher probability for severe and potentially life-threatening arrhythmic events. On the contrary, DsM-negative pts had a rather mild arrhythmic profile despite the longer f/u.

P5230 | BEDSIDE
Increased circulating mesencymal stem cells in patients with hypertrophic cardiomyopathy: correlation with left ventricular mass index

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Purpose: Stem and progenitor cells are implicated in ventricular remodelling and have great clinical significance in the pathophysiology of heart failure. However, there are limited data regarding the involvement of mesenchymal stem cell (MSCs) in the pathogenesis of left ventricular hypertrophy (LVH). The aim of this study is to investigate MSCs circulation in patients with hypertrophic cardiomyopathy (HCM).

Methods: We included 22 patients with HCM (12 males, aged 54±12 years) and 13 healthy individuals (8 males, aged 53±14 years). All subjects underwent a complete echocardiographic study. In addition, peripheral blood samples from all participants were immunostained with antibodies against the cell surface markers CD34, CD45 and CD90. Using flow cytometry, we have measured MSCs as a population of CD45-/CD34-/CD90+ cells and also as a population of CD45-/CD34-/CD105+ cells. The resulting counts were translated into the % percentage of MSCs in the total cell number of peripheral blood.
Results: Patients with HCM were shown to have increased circulating CD45-/CD34-/CD90+ and CD45-/CD34-/CD105+ cells (0.005±0.002% and 0.024±0.002%, respectively), compared to control group (0.001±0.002% and 0.01±0.006%, respectively), ($p<0.05$ for both comparisons). Both CD45-/CD34-/CD90+ and CD45-/CD34-/CD105+ cell populations revealed a strong positive correlation with left ventricular mass index ($r=0.620$, $p<0.05$ and $r=0.54$, $p<0.05$, respectively).
Conclusions: Patients with HCM were shown to have increased circulating MSCs compared to healthy individuals and this is correlated with the severity of LVH. Our findings contribute to the understanding of pathogenesis of HCM and might offer a future therapeutic target

P5231 | BEDSIDE
Fragmented QRS as a prognostic tool for predicting cardiac events in hypertrophic cardiomyopathy

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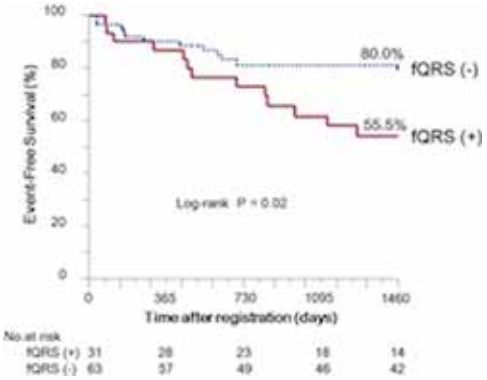
Background: Hypertrophic cardiomyopathy (HCM) is a primary disorder of the myocardium that can cause fatal cardiac events. Fragmented QRS complexes (fQRS) on a 12-lead electrocardiogram reflect intra-ventricular conduction delay and have been demonstrated to be a prognostic marker in coronary artery disease. The aim of this study was to assess whether fQRS could predict cardiac events in HCM patients.
Methods: Ninety-four HCM patients registered in Left Ventricular Hypertrophy Multicenter Registration Study in Japan from September 2008 to March 2010 were prospectively investigated. fQRS was defined by the presence of various RSR' patterns in at least two contiguous leads corresponding to a major coronary artery territory. Composite cardiac events (CCE) was defined as the occurrence of cardiac death, combined ventricular tachycardia/ventricular fibrillation, new onset atrial fibrillation and heart failure with hospitalization.
Results: Median follow-up duration was 4.6 years (interquartile range [IQR], 4.1 to 4.8 years). Mean age was 58±17 years, and 56 patients (60%) were male. fQRS was detected in 31 patients (33%). The cumulative survival of CCE at 4 years was 72.0%. In multivariate analysis, fQRS was significantly associated with CCE (adjusted HR [95% CI], 2.5 [1.01–6.4], P=0.047). At 4 years, the CCE-free survival was significantly lower in fQRS (+) group compared to fQRS (–) group (55.5% vs. 80.0%, P=0.02).



KM estimate of CCE-free survival rates.

Conclusion: These findings suggest that fQRS could be a non-invasive prognostic tool for predicting cardiac events in HCM patients.

P5232 | BEDSIDE
Hypertrophic cardiomyopathy in a large cohort of MYBPC3 c.927-2A>G founder mutation carriers

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Purpose: Most hypertrophic cardiomyopathy (HCM) cohort studies are characterized by great heterogeneity of sarcomeric protein gene mutations. The aim of this study was to determine the penetrance and clinical disease expression in a large cohort of patients and relatives carrying the MYBPC3 c.927-2A>G founder mutation, arising more than 500 years ago.
Methods: The initial study population comprised 76 probands carrying the MYBPC3 c.927-2A>G. Additionally, 223 first degree relatives accepted to undergo genetic testing and clinical evaluation, including echocardiography.
Results: Out of 223 family members, 95 c.927-2A>G mutation carriers were identified, of whom 47 (50%) were clinically affected with left ventricular hypertrophy (LVH) ≥13 mm. The penetrance was age related (34% <40 years versus 61% ≥40 years, p=0.009) and greater in males (67%) than females (35%, p=0.001). Gender specific, cumulative age related penetrance is shown in Figure 1. Neither males nor females were affected until age 17 and by age ≥80, more than 90% of individuals were affected. The degree of LVH among the relatives ranged from 13mm to 28mm, none had left ventricular outflow tract gradient ≥30mmHg at rest. The pattern of septal hypertrophy was reverse curve in 67% of patients, neutral in 21%, apical in 5.8%, and 3.5% had sigmoid septum.

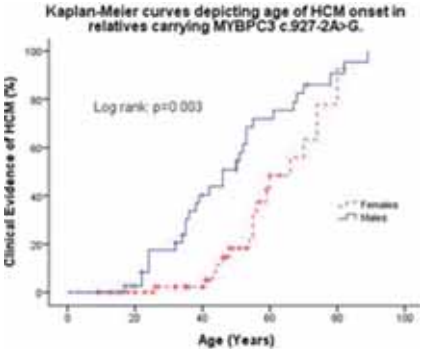

Figure 1

Conclusions: HCM related to the MYBPC3 c.927-2A>G founder mutation is mainly late onset and shows gender specific penetrance. Other genetic or environmental factors must play an important role.

P5233 | BEDSIDE
Genotype-phenotype correlation in desmosomal gene related ARVC

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Purpose: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary heart muscle disorder, mostly caused by mutations in genes encoding desmosomal proteins. The purpose of this study was to compare disease penetrance, phenotypic expression and lifetime arrhythmic risk between groups of desmocollin-2 (DSC2), plakophilin-2 (PKP2) and plakoglobin (JUP) mutation carriers.
Methods: The study population included 96 consecutive mutations carriers of DSC2 (n=28), PKP2 (n=38) and JUP homozygotes (n=30). Serial clinical workup consisting of history, physical examination, electrocardiography and echocardiography was performed. Clinical characteristics were recorded and compared between the 3 groups using chi-square and Kruskal-Wallis tests for categorical and continuous variables respectively. To determine the cumulative survival from the first major arrhythmic event (sustained ventricular tachycardia, sudden cardiac death) during lifetime, Kaplan-Meier curves were constructed and compared using the log-rank test.
Results: Penetrance and expressivity was the highest in JUP and the lowest in DSC-2 mutations (Table). Thirty-nine mutation carriers experienced the arrhythmic outcome. DSC-2 mutation carriers had a better lifetime cumulative event-free survival as compared to PKP-2 carriers and JUP homozygous carriers (p=0.022 and 0.003, respectively), whereas no difference was found between the later (p=0.55).

Clinical characteristics by genotype

Characteristics	DSC-2 (n=28)	PKP-2 (n=38)	JUP (n=30)	p-value
Age (years)	43±18	42±18	41±20	0.153
Gender, male	14 (50)	24 (63)	16 (53)	0.53
Definite ARVC	11 (39)	28 (74)	29 (97)	<0.0001
Repolarization abnormalities	6 (21)	26 (68)	22 (73)	<0.0001
Depolarization abnormalities	16 (57)	21 (55)	28 (93)	0.001
Right ventricular dysfunction	9 (32)	17 (46)	27 (90)	<0.0001
Left ventricular dysfunction	6 (21)	5 (14)	12 (40)	0.039

Values are reported as n (%) and mean±SD for categorical and continuous variables respectively.

Conclusions: Desmosomal gene related ARVC shows a gene-specific disease phenotype. JUP homozygocity was associated with higher penetrance and disease expressivity, however provided similar risk with PKP-2 heterozygocity. DSC-2 mutations were associated with lower disease penetrance, expressivity and arrhythmic risk.

P5234 | BENCH
Long-term outcome of percutaneous septal ablation for symptomatic hypertrophic obstructive cardiomyopathy

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Background and methods: We analyzed the long-term outcome of 575 consecutive patients (pts, mean age: 56±14years) treated with percutaneous septal ablation (PTSMA) for symptomatic hypertrophic obstructive cardiomyopathy (HOCM). Data were acquired by outpatient examination in our own institution or by phone contact with the pts.' local cardiologist. Pts. who could not be traced neither personally nor via their home physician or their health insurance company were considered "lost" to follow-up.
Results: In-hospital mortality was 0.9% (5 pts.). Mean CK rise was 506U/l (reference:<80). A DDD-pacemaker (DDD-PM) had to be implanted in 44 pts. 7.5 (%) for procedure-related AV conduction problems.
Follow-up was 97% complete (n=556). During follow-up (65±53 [range:0.1-204] months), 62 pts. (11%) died, of these 28 (5%) from non-cardiac, and 34 (6%) from cardiovascular causes. Overall survival was 93% at 5 years, and 90% at 10 years. A re-intervention for significant residual or recurrent outflow obstruction was necessary in 51 pts. (9%). The latter cases included, at their last follow-up visit 518 pts. (90%) were in functional class I or II. The most frequent problem was atrial fibrillation in 63 pts. (11%).
Conclusions: During long-term follow up following PTSMA, a persistent clinical improvement was observed. A second intervention (surgical or catheter-based) was needed in about 10%. The survival rates observed in this cohort compares favourably to the natural disease course in symptomatic HOCM, and seem to be equivalent to post-myectomy data.

P5235 | BENCH
High incidence of subclinical atrial fibrillation in patients with hypertrophic cardiomyopathy

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Purpose: In patients with hypertrophic cardiomyopathy (HCM) atrial fibrillation (AF) is an important prognostic parameter and often causes cardiac decompensation. Incidence of subclinical atrial fibrillation in HCM ist unknown. Moreover, it remains unclear whether parameters like septal hypertrophy, obstruction of left ventricular outflow tract (LVOT) or diastolic dysfunction contribute to higher incidence of AF. In a single centre study we evaluate the incidence of AF in patients with HCM and de novo implantation of pacemakers and implantable cardioverter defibrillators (ICD).
Methods: Over a period of 26 months 44 patients with HCM (25 with LVOT obstruction >30mmHg) received ICDs (4 VVI, 33 DDD, 1 subcutaneous ICD, 30 primary prophylaxis), pacemakers (5 DDD) or event recorder (1). To detect AF device interrogation was performed by analysing atrial high rate episodes.
Results: In 30 HCM-patients (68%) AF could be detected. In 13 patients AF was documented already prior to device implantation. During follow up (337±405 days) in a total of 17 patients newly diagnosed AF was detected only by the use of device interrogation in the absence of corresponding clinical symptoms. Neither an increasing septal hypertrophy, nor an obstruction of the LVOT or a higher grade of diastolic dysfunction is associated with the incidence of AF. However, comparable to the general population the incidence of AF in HCM patients increases with age (no AF: mean age + SD 45,1 +14,7 vs. AF: 56,7+ 12,2; $p<0.01$) and goes along with an increased CHA2DS2 VASc Score ($p<0.005$).
In the AF group 7 patients (23%) suffered from thrombembolic event vs 1 patient without documentation of AF but diagnosed coagulopathy ($p<0.01$).
In 3 ICD patients inadequate shock delivery was seen due to supraventricular tachycardia. None of them had AF before. ICD therapy due to ventricular tachycardia occurred in 6 patients (4 primary prohylaxis).,5 of them had a history of AF.
Conclusion: Interrogation of cardiac devices revealed a much higher incidence (68%) of AF in HCM patients as anticipated. According to a high rate of thrombembolic events (23%) in patients with AF early detection and treatment of AF in HCM patients should be addressed more thoroughly.

P5236 | BEDSIDE
Orthostatic blood pressure test for evaluation of syncopes and sudden cardiac death risk stratification in patients with hypertrophic cardiomyopathy

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Purpose: Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disease and associated with an increased risk of sudden cardiac death (SCD). Individual risk assessment is mainly based upon screening for malignant arrhythmias and the occurrence of otherwise unexplained syncopes, often ascribed to ventricular tachycardias (VTs). However, a proof of such arrhythmias during syncopes is usually missing. In this study, orthostatic blood pressure test and QTc prolongation were examined as prognostic factors for "adverse events" in HCM patients, here standing for SCD risk factors like cardiac syncopes, presyncopes and VTs.
Methods: 100 HCM patients (age 55.8±16.2 yrs, 61% male) were evaluated for septal wall thickness, left ventricular outflow tract gradient, QTc intervals, and NT-proBNP levels. Patients were observed for 15 months (IQR [9;20]) and syncopes, presyncopes, and VTs (24h-ECGs/ICD memories) were documented for five years retrospectively. 80 patients underwent an orthostatic blood pressure test. Logistic regression models were used for statistical analysis and results were adjusted for age and sex.
Results: Especially in patients older than 40 yrs the orthostatic blood pressure test is highly sensitive (93%; 95%-CI [76; 99]) and specific (74%; 95%-CI [58; 86]) referring to syncopes and presyncopes. A positive test result increases the chance for these events by factor 63 (95%-CI [9; 448]). The negative predictive value for the occurrence of presyncopes and syncopes was 94% (95%-CI [80; 99]) and for syncopes alone even 98% (95%-CI [88; 100]). There was no correlation between the test result and the occurrence of VTs. A prolonged QTc interval increased the chance of adverse events by factor 7 (95%-CI [2; 22]; p=0.002), but was of no further diagnostic value in addition to the orthostatic test result. The orthostatic test as well as QTc prolongation proved to be independent of the LVOT gradient, the septal wall thickness, the medication, and the NT-proBNP level.
Conclusion: The orthostatic blood pressure test proved to be valuable as an additional independent parameter in the risk assessment of syncopes and therefore possibly SCD in HCM patients. A positive result is a significant predictor for the occurrence of syncopes and presyncopes, whereas a negative result is associated with a very low risk. On the other hand, especially in patients older than 40 years of age, the test is a strong predictor for (pre)-syncopes but not for VTs. This may suggest that syncopes might rather be caused by orthostatic dysregulation than by malignant arrhythmias in elderly HCM patients.

P5237 | BEDSIDE
Risk of cardiomyopathy in persons with a family history of death from cardiomyopathy, - a nationwide cohort study

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Purpose: Cardiomyopathy risk assessments include the elicitation of any family history of cardiomyopathy or premature death. However, our understanding of how a family history of cardiomyopathy affects an individual's own risk of cardiomyopathy is limited and based on studies in highly-selected hospital-based populations. We examined the effects of various family histories of death from cardiomyopathy before 60 years of age on the risk of cardiomyopathy in first- and second-degree relatives in a nationwide population-based cohort.
Methods: Using linked Danish national register data, we constructed a cohort of 3.9 million Danes born from 1950 to 2008. We ascertained family history of death before 60 years and followed cohort members from 1977 to 2008 for cardiomyopathy diagnosed at <50 years of age. Using Poisson regression, we estimated incidence rate ratios for cardiomyopathy by family history of death before 60 years.
Results: Our cohort included 3,985,301 persons. There were 34,362 cardiac deaths before age 60 years among cohort member relatives; of those, 27,162 were ischemic heart disease deaths and 778 were due to cardiomyopathy (i.e. the person had a cardiomyopathy diagnosis and no ischemic heart disease diagnosis on the death certificate). During 89,272,960 person-years of follow-up, 3,890 persons were diagnosed with cardiomyopathy at <50 years of age; the median age at diagnosis was 38 years and 2,698 (69%) of those with cardiomyopathy were male. Cardiomyopathy deaths in first- and second-degree relatives <60 years of age were associated with 29- and 6-fold increases in the rate of cardiomyopathy, respectively. If the first-degree relative died aged <35 years, the rate of cardiomyopathy increased 100-fold. In persons with ≥2 deaths in first-degree relatives <60 years of age, the rate increased more than 400-fold. In contrast, a family history of death before age 60 years from other cardiac or non-cardiac conditions increased the rate of cardiomyopathy 3-fold at most.
Conclusion: A family history of death from cardiomyopathy in relatives <60 years of age was associated with an increase in cardiomyopathy risk ranging from 6- to 400-fold, whereas deaths due to other causes were associated with much smaller risks. Our results point to the potential outcome of pre-symptomatic screening of persons with a family history of cardiomyopathy, not least in the case of a family history of death from cardiomyopathy at a young age.

CARDIOMYOPATHIES – II

P5239 | BEDSIDE

Ventricular fibrillation post alcohol septal ablation in hypertrophic obstructive cardiomyopathy. A complication caused by dislocation of the temporary pacemaker?

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Introduction: Ventricular tachyarrhythmias are well-known complications after a transcoronary alcohol septal ablation therapy (TASH) in hypertrophic obstructive cardiomyopathy. Due to the risk of total heart block a temporary pacemaker (TPM) back-up is recommended after TASH for at least 24 h after the intervention. Dislocation of the TPM resulting in an undersensing that may cause ventricular fibrillation is a well known complication in the treatment of acute bradycardia in general.
Methods: We performed a retrospective analysis for the occurrence of post procedural ventricular tachyarrhythmias (day 1-8) of all patients treated by TASH in our center during the period 2008-2013. The monitoring attack ECG's were evaluated.
Results: A total of 389 Patients were analyzed. In 8 patients (2,1%) post procedural ventricular tachyarrhythmias occurred. In 6 cases the arrhythmia was induced by a clear R on T phenomenon caused by a dislocation of the TPM with loss of sensing. All cases appeared in the first 24 hours post the procedure and were all efficacy treated by a fast external defibrillation and inactivation of the TPM. The inactivation of the pacemaker is crucial because of otherwise frequent recurrent reinduction of ventricular fibrillation. The other cases were a sustained ventricular tachycardia with spontaneous termination and a case with spontaneous ventricular fibrillation and effective therapy by an ICD implanted pre TASH.
Conclusion: The occurrence of ventricular tachyarrhythmias after TASH is rare. In most of the cases a dislocation of the TPM with loss of sensing was the reason for ventricular fibrillation. Therefore, an accurate positioning of the TPM and a properly post procedural ECG monitoring with rapid inactivation of a dislocated TPM are essential.

P5240 | BEDSIDE

Long-term outcome after septal alcohol ablation in symptomatic patients with obstructive cardiomyopathy: a single center experience

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Purpose: Alcohol septal ablation (ASA) is now considered to be an alternative to surgical myectomy in patients with symptomatic hypertrophic obstructive cardiomyopathy (HOCM) despite optimal medical treatment. Although its short and mid-term efficacy has been established, few results are available on its long-term outcome. The aim of this study was to analyze the long-term effect of echo-guided septal alcoholisation (ASA) in a large cohort from a tertiary medical center.
Methods: 210 patients (56.6% male, 57.1±14.9 mean age) with refractory HOCM were included in our prospective ASA registry between November 1999 and May 2013.
Follow-up was performed by phone, mailing or e-mailing to the patients or referring cardiologist with parameters including new pacemaker implantation (PM), new intra-cardiac defibrillator (ICD), Re-intervention by alcohol septal ablation or surgical myectomy, NYHA functional class, medications after hospital discharge and death (cardiac and non cardiac).
Results: Alcohol septal ablation (ASA) was echo-guided in all patients and was performed via the radial route in 69.1% of cases. Procedural success rate was 92.8%. In-hospital events were observed in 16/210 cases: coronary dissection successfully treated by stenting in 1 case, ventricular fibrillation in 1 case, ventricular tachycardia in 2 cases, transient ischemic attack TIA in 2 cases, acute pulmonary oedema in 2 cases, hepatic cytolysis in 1 case, transfusion in 3 cases, fever in 2 cases and death in 2 cases (0.95%).
Mean follow-up time was 5.14 years, survival rate was 95% at 1 year, 90% at 5 years and 85% at 8 years, which did not differ from the survival rate of the same age general French population. After discharge from hospital, all-cause mortality rate was 1.75%/ per year, and cardiac-related mortality was 0.55% per year.
Age (p=0.005, OR 1.07, 95% IC 1.021-1.121) and pre-procedural septum thickness (p=0.015, OR1.209 95% IC1.038-1.407) were the only independent predictors of cardiac mortality.
Re-intervention was performed for recurrence of symptoms in 9.6% of patients: surgical myectomy in 2.03% and repeated septal alcoholisation in 7.6%. Median time to re-intervention was 2.34 years.
A Pacemaker was implanted in 10.7% of patients, and a cardiac defibrillator (ICD) in 6.9%.
Clinical improvement was demonstrated by significant NYHA score decrease (from 2.76±0.62 to 1.32±0.54, p=0.0001)
Conclusion: Alcohol septal ablation (ASA) is a safe and useful technique with good long-term efficacy.

P5241 | BEDSIDE

The role of metalloproteinases in the variants of the hypertrophic cardiomyopathy formation

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Purpose: To examine the role of matrix metalloproteinase system on the clinical course and prognosis of hypertrophic cardiomyopathy (HCM).
Materials and methods: 186 patients (88 men, 78 women) with hypertrophic cardiomyopathy were subjected, mean age was 47,1±10,0 years. The duration of the observation - 7,66±0,36 (from 3 to 28 years). 55.4% of patients had a progressive course (PC) of the disease, stable course (SC) was observed in 35.5%, 5.9% had atrial fibrillation (AF), sudden cardiac death type (SCD) of the course was seen in 2.7% and 0.5% had the end-stage type (EST). All patients were investigated according standard cardiac algorithm and genotyping of gene MMP-3 polymorphisms. Biological markers (MMP-3, TIMP-1, TIMP-2, collagen-IV) were identified in 40 patients with HCM and 39 controls.
Results: The allelic variant 6A/5A MMP-3-1171 was associated with pronounced hypertrophy of the interventricular septum (p=0.074) in patients with HCM. TIMP-1 values in HCM patients (635,7±33,1) were reduced compared with those in the control group (804,1±28,1 ng/ml; p<0,001). The concentration of the marker MMP-3 in patients with AF (37,61±21,19 ng/ml) was increased in comparison with the groups of SC (±5,47 19 ng/m, p=0,024) and PC (25,86±4.4, p=0.028). The high risk of SCD associated with genotype 6/5 polymorphism MMP-3-1171 (p=0,014). An inverse correlation were found between MMP-3 and index posterior wall thickness of the left ventricle (r= -0,313; p=0,049), and the asymmetry coefficient (r=0,337; p=0,047). For genotype 6A/5A MMP-3-1171 was characterized by an increase in the level of TIMP-1, for the other genotypes decrease its concentration (p=0.008).
Conclusion: 1. It was determined that the genotype 6/5 polymorphism MMP-3-1171 impacts the formation of hypertrophic remodeling and SCD risk in HCM. 2. The ratio disturbance of MMP-3 and TIMP-1 was found in patients with HCM with prognostically unfavorable variants of the course. 3. Polymorphism MMP-3-1171 touchs on concentration of TIMP-1.

P5242 | BEDSIDE

Assessment of left atrial function in hypertrophic cardiomyopathy and left ventricular hypertrophy in athletes

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Background: Hypertrophic cardiomyopathy (HCM) is the first cause of sudden death, and its frequency is probably more 1/500. Differentiating this condition from the nonpathological "left ventricular hypertrophy" remains a challenge. The development of pathological left ventricular hypertrophy (LVH) is associated with left atrial (LA) dilatation and dysfunction. LA strain and strain rate by two-dimensional (2D) speckle tracking are novel indices of LA function and might contribute to differentiate physiological from pathological LVH underdiagnosed HCM.
Methods: We evaluated 70 patients with nonobstructive HCM, 40 athlets and 20 healthy controls matched for age, gender, and body surface area. All patients underwent a transthoracic echocardiogram with evaluation of LA strain: s-wave (LASs); and strain rate: s-wave (LASRs) and a-wave (LASRa).
Results: LV mass index, LA volume index, and ejection fraction were comparable between patients with HCM and athletes' group. Left ventricular volumes and stroke volume were higher in athletes. likely for the mitral pick velocity of the early diastolic wave (E) and E/A ratio. HCM group has higher E/e' ratio (9.4±1.5 vs 6.7±1.8, p=0.002) Patients with HCM had a significantly lower LASs (19±8% vs. 32±7%, P<0.01), LASRs (0.55±0.2 s^{-1} vs. 1.2±0.2 s^{-1}, P<0.01), and LASRa (-0.7±0.1 s^{-1} vs. -1.1±0.3 s^{-1}, P<0.01). Among hypertrophic subjects, independent predictors of hypertrophy related to HCM were LASs and E/e' ratio.
Conclusions: LA myocardial deformation is significantly impaired in patients with HCM compared to athletes and healthy controls. LA strain and strain rate assessed by 2D speckle tracking should be incorporated in the evaluation of trained athletes with LVH and LA dilatation.

P5243 | BEDSIDE

Cardiac magnetic resonance can detect cardiac involvement in systemic sclerosis even in patients without any abnormalities in screening tests -Comparison with serological tests and other imaging-

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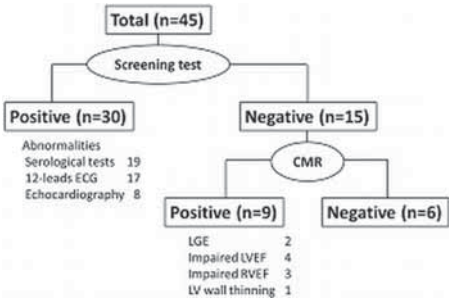
Background: The early diagnosis of cardiac involvement in systemic sclerosis (SSc) has a predictive significance. However, the definition and the diagnostic tool remain unclear. We assessed the values of cardiac magnetic resonance (CMR) for the early diagnosis by comparing with traditional screening tests.
Methods: Forty five SSc patients (56.3±14.2 years, 5/40 male/female, 16/29 diffuse/limited type, mean disease duration; 98.5 months) underwent CMR and

screening tests; serological test, 12-lead ECG and echocardiography. The abnormal CMR measures were defined from normal ranges (means±2SD) in age- and gender-matched controls by previous papers.
Results: (1) Thirty patients had some abnormalities in screening tests. The serological test identified 12 patients with NT-proBNP>125 pg/ml and 13 troponin I≧0.015 ng/ml. The 12-lead ECG showed 3 atrial fibrillation, 2 ventricular tachycardia, 3 atrio-ventricular block, 6 bundle branch blocks, 1 abnormal Q wave, and 6/3 electrical LV/RV hypertrophy. The echocardiography revealed 4 low LVEF, 3 asynergy, 1 LV hypertrophy, 5 LV diastolic dysfunction, and 3 pulmonary arterial hypertension. (2) Twenty five patients had some CMR abnormalities including 9 late gadolinium enhancement (LGE), 3 asynergy, 6 LV wall thinning, 3/1 LV/RV hypertrophy, 4/3 LV/RV dilatation, and 13/10 low LVEF/RVEF. (3) Nine of 15 patients (60%), who showed no abnormalities in screening tests or Medsger Severity Index=0, demonstrated some CMR abnormalities (Figure).



Comparison with screening tests and CMR.

Conclusions: CMR abnormalities were frequently identified in patients with SSc. CMR is useful for LV/RV early systolic dysfunction and myocardial fibrosis which could not be detected by screening tests. Clinicians should examine CMR for the early diagnosis of cardiac involvement in addition to screening tests.

P5244 | BEDSIDE
Serum MMP-9 as a quantitative biomarker for myocardial fibrosis in patients with hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disease and associated with an increased risk of sudden cardiac death (SCD). Myocardial fibrosis is one fundamental pathogenic substrate for cardiac arrhythmias. Therefore late gadolinium enhancement (LGE) shown by contrast cardiac magnetic resonance imaging (CMR) is an important risk factor of SCD as well as the occurrence of syncopes and ventricular tachycardias (VTs). Certain matrix metalloproteinases (MMPs) can impact on collagen turnover and are therefore relevant to myocardial fibrosis. These serum biomarkers were correlated with the amount of myocardial LGE and the occurrence of cardiac syncopes and VTs in HCM patients.
Methods: 54 HCM patients (age 55.9±14.3 yrs, 27 women) were investigated by CMR. After injection of 0.2 ml/kg gadolinium the amount of fibrotic tissue was assessed in percentage of the total myocardial mass of each patient. A myocardial signal intensity >2 standard deviations above remote myocardium was regarded as LGE. Serum concentrations of MMP-9, MMP-2 and its corresponding tissue inhibitor TIMP-1 were measured using ELISA-Assays (Amersham Pharmacia Biotec®). Linear regression models were used for statistical analysis.
Results: The mean MMP-9 concentration was 53.7±34.9 ng/ml. Those nine patients (16.7%) without LGE in CMR had a lower MMP-9 value (29.6±14.2 ng/ml), than patients positive for LGE (59.8±36.2 ng/l, p=0,01). The mean fraction of fibrosis was 13.3±10.3% in these 45 patients and in each patient showing fibrosis MMP-9 was enhanced compared to healthy controls. Hence, an increased value of MMP-9 is highly sensitive (92%; 95%-CI [73; 99]) for the occurrence of myocardial fibrosis (23% specificity; 95%-CI [10; 42]). With a mean increase of 6.3g (95%-CI [5;8]) of fibrosis per ten units of MMP-9 ($p<0.001$), this association was stronger in women than in men (2.7g (95%-CI [0.4;5]/10 units MMP-9; p=0.023) and was also a gender dependent predictor for the occurrence of syncopes and VTs. While the MMP-9/TIMP-1 ratio also positively correlated with the amount of fibrosis, no association could be detected for MMP-2 or TIMP-1 alone. All effects were adjusted for age, sex and myocardial mass.
Conclusion: Serum MMP-9 levels are associated with the amount of myocardial fibrosis detected by LGE in cardiac MRI in HCM patients. Hence, MMP-9 is an easily to obtain serum biomarker, which seems to be suitable for predicting myocardial fibrosis and possibly SCD risk factors such as syncopes and VTs especially in women with HCM.

P5245 | BEDSIDE
Impact of latent obstruction on exercise tolerance in hypertrophic cardiomyopathy

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Background and aims: Reduced exercise tolerance is variably present in hypertrophic cardiomyopathy (HCM). We sought to evaluate the impact of exercise induced obstruction on exercise performance and the determinants of functional capacity in this subgroup.
Methods: The study sample included 144 HCM patients with normal ejection fraction (mean age: 51±14, males 63%), enrolled from 2007 to 2012 with a complete clinical assessment, including rest and stress echocardiography and cardiopulmonary exercise test (CPET) with impedance cardiography.
Results: At baseline 41 patients had an obstruction at rest (28%, group 1), 33 (23%) presented a latent obstruction (group 2) while 70 (49%) were non obstructive (group 3). Patients with rest obstruction showed a reduced peak VO2, in comparison with the other two subgroups (group 1: 22.4±7.7 ml/kg/min; group 2: 28.9±11.7 ml/kg/min; group 3: 28.3±10.5 ml/kg/min, p=0.005). VE/VCO2 slope was similar in the three subgroups (group 1: 30.7±6.7;group 2: 28.2±5.8; group 3: 28.3±6.0, p=0.17) as well as peak CI (group 1: 9.6±3.2 vs. group 2:11.1±4.5 vs. group 3: 10.3±3.5 l/min/m^2, p=0.29). In the latent subgroup the main determinants of peak VO2 at a multivariate analysis were age (r=-0.66, $p<0.001$) and relative wall thickness (r=-0.39, p=0.03), while neither gradient at stress nor the Δ gradient between rest and stress reached the statistical significance.
Conclusions: Patients with latent obstruction and non-obstructive have a similar exercise tolerance. In patients with exercise induced obstruction the reduction of functional capacity is not related to the peak stress gradient, but to relative wall thickness and age.

P5246 | BEDSIDE
Clinical profile and in-hospital course of patients with Takotsubo cardiomyopathy and right ventricular involvement

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Purpose: Is to describe the prevalence, clinical findings, echocardiographic features and in-hospital course of patients with tako-tsubo cardiomyopathy (TTC) and right ventricular involvement (RVi).
Methods: The study population consisted of 495 consecutive patients (mean age 69.1±11.5 years, 91% female) prospectively enrolled in Tako-tsubo Italian Network (TIN). Clinical and demographic characteristics, as well as, ECG and laboratory findings were collected. Transthoracic echocardiography was performed within 6 hours of hospital admission and right ventricular morphology was assessed visually from all available echocardiographic windows. Patients (pts) were divided into two groups according to the presence (group A) or absence (group B) of RVi.
Results: RVi was detected in 53 pts (10.7%) and there are no significant differences in age (mean age 68.2±13.9 vs 69.3±11.2 years), and sex prevalence (92% vs 91% female) between the two groups. chronic obstructive pulmonary disease (23 vs 15%; p=0.006), other non-acute cardiac disease (27 vs 13%; p=0.008) and history of cancer, included previous treatment with chemotherapeutic agent (19 vs 9%; p=0.034) as well as total associated comorbidities were more frequent in group A (1.25 vs 0.89; p=0.032). The association of chest pain with dyspnea was more prevalent in group A (25 vs 5%; $p<0.001$), whereas isolated chest pain was the most common presenting symptom in patients without RVi (55 vs 74%; p=0.003). Any significant difference concerning the ECG changes at admission was found between the two groups. Left ventricular ejection fraction (35.7±6.6 vs 36.8±7.1%; p=0.306) and E/e' ratio (11.6±4.1 vs 10.9 vs 3.9; p=0.405) were not significantly different between the two groups. Tricuspid annular plane systolic excursion (16.7±4.3 vs 19.6±4.0 mm; p=0.003) and RV area change were significantly lower in group A compared to group B (26.7±4.2 vs 41.1 vs 4.3%; $p<0.001$). Conversely pulmonary artery systolic pressure was higher (43.7±14.6 vs 39.6±9.8 mmHg; p=0.034) in group A. Moderate to severe mitral regurgitation (36 vs 18%; p=0.02), major adverse events (acute heart failure and cardiogenic shock) were prevalent in group A pts (37 vs 17%; p=0.001).
Conclusion: Patients with TTC and RVi have a different clinical profile associated with several comorbidities and represent a subset of patients at higher risk of in-hospital complications such as acute heart failure and cardiogenic shock. Thus aggressive therapeutic strategies should not be neglected or postponed in this setting.

P5247 | BEDSIDE
The impact of gender in a desmosomal mutation associated ARVC population

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Purpose: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is mostly caused by mutations in genes encoding desmosomal proteins. The purpose of this study was to investigate the role of gender in an unselected desmosomal mutation carrier population in relation to penetrance, disease expressivity and lifetime arrhythmic risk.
Methods: The study population included 105 desmosomal mutation carriers of plakophilin-2 (n=38), desmocollin-2 (n=28), desmoplakin (n=6), plakoglobin homozygocity (n=30) and digenic heterozygocity (n=3). Serial clinical work-up consisting of history, physical examination, electrocardiography, and echocardiography was performed. Clinical characteristics of each group were recorded and compared between the 2 groups, using the chi-square and Mann-Whitney U tests for categorical and continuous variables, respectively. To determine the cumulative event free survival from the first major arrhythmic event (sustained ventricular tachycardia and sudden cardiac death) during lifetime, Kaplan-Meier curves were constructed, stratified by gender and compared with the log-rank test.
Results: Of the 105 subjects, 56 were male and 49 female. Gender was equally represented as suggested by the chi-square goodness-of-fit test ($\chi 2$=0.467, p=0.5). Clinical characteristics and their comparison between males and females are presented in Table 1. Forty-three mutation carriers experienced the arrhythmic outcome. Males exhibited a significantly lower cumulative arrhythmia-free survival (p=0.002) as compared to females.

Clinical characteristics by gender

Characteristics	Males (n=56)	Females (n=49)	p-value
Age (years)	39±19	44±17	0.22
Definite ARVC	44 (79)	32 (65)	0.13
Repolarization abnormalities	34 (61)	23 (47)	0.16
TAD ≥55 ms	21 (46)	23 (50)	0.68
Epsilon waves	19 (34)	9 (18)	0.07
Right ventricular dysfunction	37 (66)	18 (38)	0.004
Left ventricular dysfunction	18 (32)	10 (21)	0.20

Values are reported as n (%), mean±SD for categorical and continuous variables respectively.

Conclusions: Male carriers of ARVC-associated desmosomal gene mutations developed more frequently right ventricular functional-structural alterations and exhibited higher arrhythmic risk.

P5248 | BEDSIDE
Clinical significance of persistently-increased heart rate despite optimal pharmacotherapy to predict heart failure prognosis independent of improved left ventricular ejection fraction

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Purpose: Increased heart rate (HR) has been known as a poor prognostic factor in heart failure (HF) patients with systolic dysfunction. We thought to clarify whether persistently high HR has also prognostic value in patients with subsequent functional improvement after optimal pharmacotherapy (OPT).
Methods and results: We enrolled 85 consecutive newly-diagnosed non-ischemic dilated cardiomyopathy (ND-DCM) patients with left ventricular ejection fraction (LVEF) <35% and sinus rhythm at baseline. HR and LVEF were serially evaluated for 12 months follow up after OPT. Among baseline variables, multivariate analysis indicated that higher HR was an independent predictor of combined cardiac events (CEs) including HF hospitalizations and major ventricular arrhythmias (adjusted hazard ratio 1.1, 95% confidence incidence 1.0-1.2, P<0.01). The receiver-operating characteristics curve demonstrated that baseline HR was a significant predictor, with an area under curve of 0.72 for subsequent CEs and a best cut-off value of 66 bpm. The patients were divided into three groups stratified by HR at baseline together with that at 12 months after OPT: patients with persistently high HR of ≥66 bpm (n=24, 28%, HH) during the 12 months, those with baseline HR ≥66 bpm but decreased HR of <66 bpm at 12 months (n=14, 17%, HL), and finally those with persistently low HR of <66 bpm (n=47, 55%, LL). Kaplan-Meier survival curves demonstrated that HH had significantly higher incidence of CEs than HL or LL (P<0.01, Figure), whereas there was no significant differences in improvement of LVEF during the 12 months +(17±3)% in HH, +(22±4)% in HL, vs. +(19±2)% in LL (P=0.48).
Conclusions: Persistently high HR after OPT is a strong risk for cardiac events irrespective functional ventricular recovery in ND-DCM.

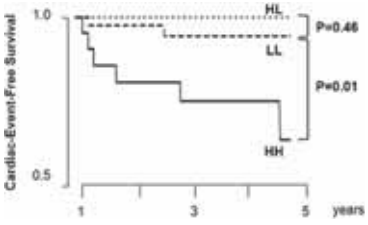

Figure 1. Kaplan-Meier survival curves.

CARDIOMYOPATHIES – III

P5250 | BEDSIDE
Three-dimensional myocardial strain patterns in patients with physiological and pathological hypertrophy and preserved left ventricular systolic function: a comparative study

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Purpose: This study aimed to explore the utility of three-dimensional speckle-tracking strain (3DSTE) to discriminate functional adaptations of the left ventricle (LV) in physiological versus pathological LV hypertrophy (LVH).
Methods: A total number of 286 subjects, including 50 HCM patients (52±15 yrs) with preserved ejection fraction (LVEF 67±7%), 25 professional athletes (35±13 yrs) and 211 healthy volunteers (44±15 yrs) were examined using Vivid E9 scanner. LV 3D volumes (end-diastolic, EDV, end-systolic, ESV), mass, peak global and segmental strain (longitudinal, 3DLε; circumferential, 3DCε; radial, 3DRε; area, 3DAε) were measured with EchoPac BT12. Global strain dispersion index (εDI) was calculated for all 3D strain parameters as the average of the standard deviation values of segmental strain in all 17 LV segments.
Results: Adequate tracking for global 3D strain analysis was achievable in 248 (87%) datasets (temporal resolution 36±7 vps). HCM pts had significantly lower segmental and global peak 3DLε, 3DRε and 3DAε compared with athletes and controls (p<0.001 for all), while 3DCε was similar among groups (p=0.7). Strain dispersion index (εDI), a measure of regional contractile heterogeneity, was higher in HCM compared with the other groups (Table). On receiver operator characteristics (ROC) analysis, 3DLε had the best discriminatory ability among all strain parameters to distinguish HCM from athletes (area under curve, AUC=0.80, p<0.001) or controls (AUC=0.84, p<0.001). However, 3D LV geometry (LV mass/EDV) and indexed LV mass were better suited than 3DLε to differentiate the athlete's heart from HCM (AUC 0.98 and 0.95, respectively).

Strain dispersion index (εDI) comparison

	HCM (n=50)	Athletes (n=25)	Healthy subjects (n=211)
3DLε	6.65	3.80*	4.17*
3DCε	6.95	5.10	4.94*
3DAε	10.16	5.56*	6.09*
3DRε	22.31	13.14*	14.10

*p<0.01 versus HCM.

Conclusion: Three-dimensional echocardiography allows a fast and comprehensive characterization of LV geometry and myocardial deformation in subjects with LVH, which may help to differentiate HCM from athlete's heart. Impairment of 3D longitudinal strain with a high strain dispersion index favor the diagnosis of HCM.

P5251 | BEDSIDE
Extensive overlap of myocardial fibrosis and regional sympathetic nervous dysfunction predicts long-term clinical outcome in patients with idiopathic dilated cardiomyopathy

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Purpose: Myocardial fibrosis detected by late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) and sympathetic nervous dysfunction detected by 123I-metaiodobenzylguanidine (MIBG) are associated with worse outcome in idiopathic dilated cardiomyopathy (IDCM) patients. However, relationship remains unknown. We sought to compare the distribution of LGE and defect locations of MIBG and to investigate the association of them with long-term adverse events.
Methods: We studied 85 IDCM patients (59±15 years, LVEF 31±8%) with positive LGE by CMR. They underwent MIBG, and defect locations in SPECT as area with relative activity<60% of maximum were investigated. Distribution of positive LGE and MIBG defect were distinguished at apical, anterior, septal and lateral regions except for inferior region (due to MIBG image attenuation) and then compared. Heart/mediastinum ratio in delayed phase (delayed H/M) was calculated from planner image. Cardiac death and heart failure hospitalization were defined as events (follow-up 2279±819 days).
Results: LGE distributed mainly in inter-ventricular septum, whereas spread more diffusely into other segments in part. Defect in MIBG was observed in 76 cases (89%). There was no overlap between CMR and MIBG (non overlapping group) in 42 (49%), overlap only at septum (partially overlapping) in 30 (35%), and overlap at spread into other segments (largely overlapping) in 13 (16%) cases, respectively. Among three groups, largely overlapping group was associated with worse outcome (P<0.01) and lowest delayed H/M (P<0.01).
Conclusions: Extensive overlap of myocardial fibrosis and regional sympathetic

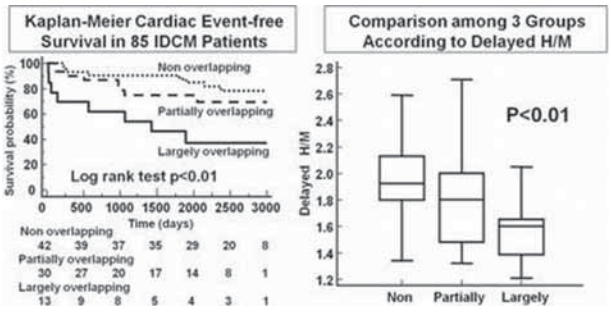

Figure 1

nervous dysfunction predicts poor clinical outcome in IDCM. Combination of CMR and MIBG may be useful to stratify the future risk of IDCM.

P5252 | BEDSIDE
A founder MYBPC3 frameshift mutation results in HCM with a severe prognosis and high risk of sudden death in middle-aged patients

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Purpose: Previous studies reported a delayed expression and clinically benign outcome in hypertrophic cardiomyopathy (HCM) patients carrying MYBPC3 mutations. The aim of this study was to evaluate the clinical characteristics, penetrance and prognosis of HCM patients carrying a frequent founder mutation in MYBPC3.
Methods: Study population included 97 HCM probands. All of them were screened for MYBPC3 mutations and 19 were found to have the same frameshift mutation (c.912_913delTT, p.F305PfsX27). Pedigree analysis, including both clinical evaluation and genotyping, was performed. Carriers of the identical mutation were genotyped with 4 microsatellites and 9 SNPs flanking this gene in order to understand if it was a founder mutation. Clinical characteristics and cardiovascular events were compared between the frameshift mutation carriers (Group 1), other MYBPC3 mutation carriers (Group 2) and patients negative for MYBPC3 mutations (Group 0), using univariate and multivariate analyses.
Results: The MYBPC3 frameshift mutation c.912_913delTT (p.F305PfsX27), was found in 19 (19.5%) index cases (14 males and 5 females). Among 81 relatives belonging to 14 apparently unrelated families, 45 (20 males and 25 females) resulted to be mutation carriers and 29 of them (17 males and 12 females) had HCM. Haplotype analysis confirmed a common founder ancestor in these families. Disease penetrance was incomplete (64.4%) and was greater in males than females (85% versus 48%, p=0.009). Eleven (38%) affected mutation carriers were diagnosed between 30 and 40 years old. Probands carrying this frameshift mutation had less maximal hypertrophy at last control (p=0.05) compared to patients with other MYBPC3 mutations (Group 2). During a mean follow-up of 10 years they experienced more frequently non-sustained ventricular tachycardia (p=0.01), underwent ICD implantation (p=0.02) and showed a worse prognosis for sudden cardiac death (SCD) or aborted SCD (p=0.01) compared with Group 0 patients.
Conclusions: The founder MYBPC3 mutation carriers have a high probability to develop the disease between 30 and 40 years of age, with an increased risk if they are men, and they show a significantly reduced survival after the fourth decade of life when compared to patients without MYBPC3 mutations. These findings are of relevant importance for the genetic counseling and therapy, considering the high frequency and poor prognosis associated with this founder mutation.

P5253 | BEDSIDE
Long-term effect of corticosteroid therapy in patients with cardiac sarcoidosis

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Purpose: Cardiac involvement is the worst prognostic determinant in patients with sarcoidosis, however, the long-term effects of corticosteroid therapy on clinical outcomes in patients with cardiac sarcoidosis (CS) remains unclear.
Methods: We examined 86 consecutive patients who were definitively diagnosed as CS during past 35 years in our institution. Patients were divided into two groups based on the presence or absence of corticosteroid therapy at diagnosis.
Results: Corticosteroid therapy was performed in 70 patients. Patients with corticosteroid therapy had lower age and higher incidence of positive findings in gallium scintigram (Ga) at diagnosis than those without. LV ejection fraction (LVEF), angiotensin converting enzyme (ACE) and lysozyme, BNP levels, other cardiovascular medications and therapies were comparable between the two groups. During the follow-up (8.3±5.6 years), corticosteroid therapy was associated with lower long-term adverse events (overall, P=0.005; cardiac death, P=0.76; symptomatic arrhythmias, P=0.91; heart failure (HF) admission, Figure A), and greater % increase in LVEF (7.3±36.0% vs -16.7±34.8%, Figure B). Multivariate analyses showed that corticosteroid therapy (HR 0.41, 95% CI 0.20-0.91, P=0.029) was an independent negative determinant of long-term adverse events among variables including age, gender, baseline LVEF, and positive Ga findings. Subgroup analyses showed corticosteroid therapy was associated with better clinical outcomes in all subgroups (age, gender, baseline LVEF, ACE and lysozyme, BNP levels, finding of Ga).

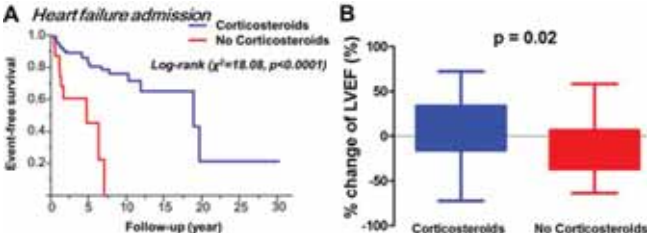

Figure 1

Conclusions: Corticosteroid therapy might have beneficial effects on long-term clinical outcomes by reduction of HF admission, with retarding progression of left ventricular systolic dysfunction in patients with CS.

P5254 | BEDSIDE
Discriminating hereditary transthyretin cardiomyopathy from hypertrophic cardiomyopathy using an echocardiographic and ECG based classification tree

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Objectives: Hereditary transthyretin amyloidosis (ATTR amyloidosis) with cardiac involvement could easily be misdiagnosed as hypertrophic cardiomyopathy (HCM) due to echocardiographic similarities, as both diseases are characterized by increased left ventricular myocardial thickness. The aim of this study was to create a classification tree based on ECG and echocardiography that could identify ATTR amyloidosis patients.
Methods: Thirty-three patients with ATTR amyloidosis and cardiac involvement and 30 patients with diagnosed HCM were included in the study. Retrospective analyses of echocardiographic variables were analysed, including measurements of dimensions, systolic and diastolic left ventricular (LV) function. Voltage, PQ- and QRS duration was analysed from ECG. LV deformation and entropy were measured in order to assess myocardial intrinsic function and texture.
Results: Two classification trees were created, one only based on echocardiographic features accessible in everyday practice. The second tree was based on multimodal features: conventional and advanced echocardiography and ECG. The multimodal tree presented with the highest sensitivity (0.938) and specificity (0.821) and included two branches. QRS voltage >30 mm classified patients as HCM. Subjects with voltage <30 mm were classified as HCM if interventricular septal and posterior wall thickness ratio (IVSt/PWt) were >1.6 and as ATTR if IVSt/PWt <1.6.

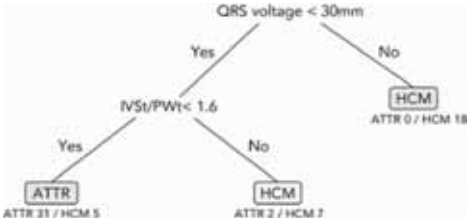

Figure 1

Conclusion: Our study proposes an easy interpretable classification tree for the differentiation between HCM and ATTR amyloidosis, presenting with higher sensitivity and specificity than any single variable associated with ATTR amyloidosis. Our combined echocardiographic and ECG model could increase the ability to identify ATTR cardiac amyloidosis in clinical practice.

P5255 | BEDSIDE
Heart rate and blood pressure responses to exercise in familial amyloid polyneuropathy - impact on the prognosis

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The responses of heart rate (HR) and blood pressure (BP) to exercise reflect cardiac autonomic balance and appear to be attenuated in patients with familiar amyloid polyneuropathy (FAP) V30M-TTR, even in the pre-clinical stages of the

disease. However, it is unknown whether these variables give significant prognostic information.
Objective: To evaluate the prognostic value of changes in HR and BP during exercise test (ET).
Methods: Of the 239 V30M-TTR mutation carriers followed annually, 155 (42±12 years; 53.5% female) asymptomatic or mild symptomatic who were able to perform exercise (Bruce protocol) were enrolled. HR and BP were recorded at rest, at each stage of exercise and during recovery. The chronotropic index [(CI); normal >0.8] and the HR recovery (HRR) at one minute after cessation of exercise (normal >18bpm) were calculated. To examine the risk of death from any cause we used multivariate Cox regression analysis, adjusted for age, and Kaplan-Meier survival analysis.
Results: Over a median follow-up of 36 months, the ET was repeated periodically until the patients' physical capacity allowed, for a total of 464 tests. The mean exercise duration was 9.3±2.8 minutes (11.9±4.9 METS). During follow-up, eight patients (5.2%) died. Multivariate Cox regression (backward conditional method) adjusted for age showed that the risk of death increased with baseline systolic BP [Hazard Ratio: 1.09, 95% IC 1.03-1.16, P=0.005] and correlated inversely with baseline diastolic BP (Hazard ratio: 0.88, 95% IC 0.80-0.96, P=0.006). In addition, the risk was inversely proportional to the peak HR (Hazard ratio: 0.95, 0.93-0.97, P<0.001) and increased with HR at the 1st minute of recovery (Hazard ratio: 1.07, 95% IC 1, 03-1.17, P<0.001). In fact, the risk of death was nearly four times higher in individuals with HRR abnormality (Hazard ratio: 3.81, 95% IC 1.15-12.67, P=0.029), whereas CI had no prognostic value.
Conclusion: In asymptomatic or mildly symptomatic patients with V30M-TTR, the changes in blood pressure induced by exercise have no prognostic value. Only peak HR, HR at the 1st minute of recovery and HRR have prognostic impact.

P5256 | BEDSIDE
What is the optimal duration of pacemaker (PM) backup after TASH in HOCM? Results from a prospective study in 139 patients

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Background: Even after an uneventful TASH a total heart block may occur within the first days after the intervention. Therefore, telemetric monitoring is recommended at least for 7 days. After we identified risk factors (RF) for the total heart block in 2007 we publicated our approach for the postprocedural pacemaker management: In patients with a retrograde AV nodal block after TASH and at least one additional RF (age>58 years, QRS-interval>120ms, intraprocedural total heart block) we recommended to extend the temporary pacemaker period from 24 h up to 7 days.
Aim of the study: Prospective examination of this PM-regime under real-live conditions.
Methods: In 139 consecutive patients we analyzed the risk for total heart block after TASH. Only patients with atypical HOCM and patients who already had a PM or ICD pre TASH were excluded. We examined in particular whether the patients were under PM protection at the time of the occurrence of a post-procedural III° AV-block or not.
Results: 19 (13.7%) of the patients experienced a total heart block after TASH (18 within the first 4 days and one patient on day 7 after TASH). According to our regime we treated 71 patients with low risk (0 or 1 RF) with a PM for only 24 h and 68 high-risk patients (retrograde AV block + at least one additional risk factor) with a pacemaker back-up for several days (average: 4.8 days). The risk for PM-dependency after TASH was more than twice as high in the high-risk group (18%) compared to the low-risk group (7%). During the occurrence of III° AV-block, 71% of the low-risk and 75% of the high-risk patients were under the protection of the temporary PM. In the other cases a rescue temporary PM could be placed until permanent PM-implantation was performed without complications.
Conclusion: For the first time, risk factors for the occurrence of a total heart block after TASH could be confirmed in a prospective study. The risk for III° AV-block was 2.6 times greater in the high-risk group compared to the low-risk group. Risk stratification and optimization of the duration of PM-back-up improves the safety after TASH and increases the rate of patients who are under PM protection when total heart block occurres from 26% to 73%. According to these data we recommend to place a temporary PM for 4 days in patients with high risk for total heart block after TASH. In low-risk patients it appears to be adequate to leave the PM lead for 24 h.

P5257 | BEDSIDE
Usefulness of longitudinal strain to predict major cardiac events in patients with hypertrophic cardiomyopathy

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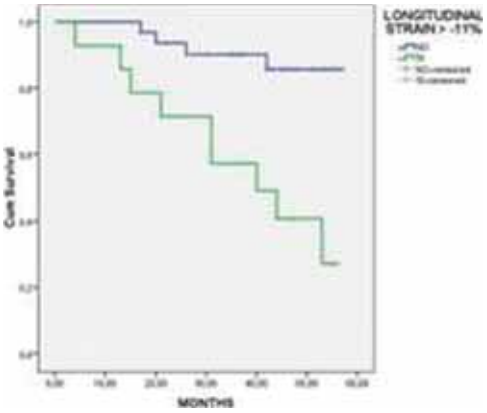
Introduction: Many studies have reported that the presence of fibrosis in left ventricular myocardium (LVM) as late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR) has prognostic value for the occurrence of MACE in HCM patients. Low global longitudinal strain (GLS) values by speckle-tracking (ST) have been related to the presence of fibrosis on CMR in HCM patients. Therefore we speculated that GLS values might independently predict prognosis of HCM patients.
Methods: We included 51 HCM patients, 48.1% ICD carrier. Medical records were checked for occurrence of a MACE, including cardiac death, sustained ventricular tachycardia and hospital admission due to cardiac cause. Events were analyzed using Kaplan–Meier curves.
Results: Follow-up was completed in 98% of patients with a mean of 39.33±13.7 months. Long S was independently associated with MACE in our HCM cohort (OR 1.16 (1.01-1.3) while classic echocardiographic parameters and SCD risk factors were not. ROC curves of GLS revealed AUC of 0.71 (0.54-0.87, p 0.017) and the best cut off point was -11% (sensitivity 71%, specificity 72%). Kaplan-Meier curves by strain >-11% are shown in the picture below.



Event-free survival curves.

Conclusion: Speckle tracking derived GLS with a cut-off point of -11% provides useful non invasive information to accurately predict MACE in HCM. This clinically promising parameter might be added to classic risk factors to improve risk stratification in patients with HCM.

P5258 | BEDSIDE
Inflammation and persistence of viral activity in endomyocardial biopsy specimens of patients with left ventricular dysfunction predicts unfavourable outcomes

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Purpose: A significant proportion of patients (pts) with non-ischemic heart failure (NICHF) has viral persistence and/or inflammation in their endomyocardial biopsy (EMB) specimens. EMB is still not routinely used in the evaluation of heart failure pts. The aim of our study was to examine the proportion of viral persistence and/or inflammation and to determine the prognosis in pts admitted for evaluation of NICHF pts by analysing EMB specimens.
Methods: 100 patients with clinically suggested NICHF underwent coronary angiography and endomyocardial biopsy. EMB specimens underwent immunohistological assessment. Polymerase chain reaction (PCR) was performed to detect the genomic sequences of enterovirus (EV), adenovirus (ADV), human cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), parvovirus B-19 (PVB-19), influenza A and B viruses, Chlamydia (trachomatis, psittackie, pneumoniae) and Coxiella burnetii. All pts had markedly reduced LVEF: (25±7%), increased NT-proBNP values (range: 1500-3500pg/ml) and symptoms of heart failure (NYHA functional class II–IV).
Results: In 90 pts viral genome was detected. Chlamydia Trachomatis (n=35), Chlamydia psittaci (n=1), HSV-6 (n=1), Coxsackie B3 (n=2) and CMV (n=1). Coinfections with Chlamydia trachomatis and either HSV-1/HSV-2 or HSV-6 were present in 20 biopsy specimens while coinfection with ParvoB-19 and HSV-1/HSV-2 in 20 biopsy specimen. Inflammation (>14 lymphocytes or macrophages/mm^2, WHF criteria) was observed in 30 patients. Patients were divided into 4 groups: group 1 consisted of pts without any inflammation or virus detection (n=10), group 2 of pts with autoreactive myocarditis (virus-negative, but inflamed myocardium) (n=10), group 3 of virus-positive pts without inflammation (n=29) and pts with virus-positive inflammed myocardium formed group 4 (n=51). All major cardiovascular events [MACE; cardiovascular death (n=6), assist device implantation (n=10), heart transplantation (n=10) and re-hospitalisation due to cardiac decompensation (n=15)] during one year were recorded. Kaplan-Meier curves demonstrated an increased amount of cardiovascular events in group 4 when compared to the other groups. When patients were divided according to viral status, patients without virus detection tended to have fewer cardiovascular events compared to patients with virus persistence.
Conclusion: Viral persistence in pts with NICHF was associated with increased MACE. Pts with virus-positive inflammed myocardium had the worse short-term prognosis. Data from EMB in pts with reduced left ventricular function is of prognostic relevance.

P5259 | BEDSIDE

Right atrial enlargement is a marker of left ventricle diastolic dysfunction in patients with hypertrophic cardiomyopathy

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Introduction: Left atrial (LA) enlargement is an established marker of poor prognosis in several cardiovascular diseases, including hypertrophic cardiomyopathy (HCM). Recently, right atrial (RA) enlargement has been associated with right diastolic dysfunction in heart failure. There are no data describing the RA in HCM. This study aimed to characterize RA size and function in HCM patients, and to evaluate the specific characteristics of those with increased right atrial volume index (RAVI).
Methods: HCM patients were prospectively enrolled and submitted to a transthoracic echocardiographic examination. Atrial volumes were calculated in ventricular end systole and end diastole, through the Simpson's method and indexed to body surface area. Right atrial ejection fraction (RA EF) was calculated through the formula (major RAV- minor RAV)/major RAV.
Results: 53 patients, 62.3% men, mean age of 48.7±17.7 years were included. Mean RAVI was 21.8±9.0 ml/m^2 and mean RA EF was 48.7±17.6%. Twenty three patients (43%) met the current guidelines criteria for RA enlargement (RAVI >21 ml/m^2). Patients with increased systolic RAVI were more commonly men (82.6 vs 41.1%; p=0,011), presented the septal asymmetric HCM subtype (82.6 vs 51.8%; p=0.022), had higher systolic LA volume index (LAVI) (48.6±22.5 vs 35.8±13.4 ml/m^2, p=0.030) and smaller RA EF (40.6±17.6 vs 50.4±16%, p=0.048) and LA EF (38.4±13.4 vs 49.3±10.1%, p=0.006), without significant differences regarding left ventricular (LV) volumes or LV EF. Patients with higher RAVI had lower late transmitral flow velocity (A wave 6±0.02 vs 8±0.04 cm/s, p=0.008) and higher E/A ratio (1.7±0.7 vs 1.2±0.5, p=0.009), without significant differences on tissue Doppler velocities or E/E′ ratio. Additionally, these patients had higher LAVI/A′(7.7 vs 5.3, p=0.030), a new marker of severe left diastolic dysfunction. The groups had similar transtricuspid flow, tricuspid annular systolic excursion, right ventricle tissue Doppler velocities and E/E′ratio. Univariate logistic regression, showed significant association between increased RAVI and A wave (p=0.016), E/A ratio (p=0.017), LAVI/A′(p=0.024), LA EF (p=0.015) and septal asymmetric subtype (p=0.027). Multivariate logistic regression model, showed that septal asymmetric subtype was the only variable independently associated with increased systolic RAVI (p=0.021).
Conclusions: Increased systolic RAVI is frequent in patients with HCM and it is associated with LV diastolic dysfunction. Presence of septal asymmetric HCM type was the only independent predictor of increassed RAVI.

NON-INVASIVE ELECTROPHYSIOLOGY

P5261 | BEDSIDE

Magnetocardiographic analysis of ventricular repolarization in hypertrophic cardiomyopathy: the role of heterogeneous repolarization on the occurrence of lethal ventricular tachyarrhythmias

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Background: The mechanism for lethal ventricular arrhythmias (VA) in hypertrophic cardiomyopathy (HCM) is poorly understood. Hypertrophy causes heterogeneous repolarization (Rep), increasing arrhythmia vulnerability, however, few studies have evaluated its role on the genesis of VA. We evaluated depolarization (Dep) and Rep process and their role for VA using multi-channel magnetocardiography (MCG) with high spatial resolution.
Methods: In 105 HCM patients with QRS <120ms, we recorded 64-Ch MCGs (1kHz), yielding 2-D map. On QRS map, we defined heterogeneous Dep characterized by divergent multi-directional LV currents according to our previous study. Current pattern during Rep was analyzed on ST-T (Rep) map. We also 25 normal volunteers and 15 subjects with isolated LBBB (iLBBB) with normal LV function.

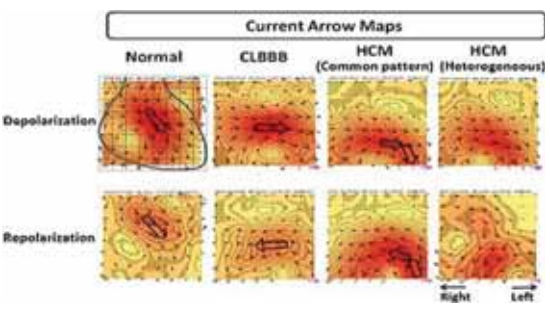

Figure 1

Results: (1) Heterogeneous Dep was recognized in 29/105. In most of HCM patients (78/105), main Rep current was oppositely directed to that of Dep, which was analogous to iLBBB. However, some exhibited heterogeneous Rep, defined when extraordinary currents unexplained by Dep (n=12) or simultaneous extracurrents were recognized (n=26). (2) During the follow-up (2.5 years), 10 experienced VA events (1 SCD, 4 sustained VT/VF, and 5 appropriate ICD discharge). Events more frequently occurred in patients with (8/29, 28%) than without (2/76, 3%) heterogeneous Dep (p<.001), but were not associated with Rep patterns (heterogeneous in 5/38 vs. others in 5/67).
Conclusions: Most of HCM patients showed altered but homogeneous repolarization (main current was oppositely directed to that of depolarization, similarly in isolated LBBB), whereas some exhibited heterogeneous repolarization. However, VA was associated with heterogeneous depolarization, but not with heterogeneous repolarization.

P5262 | BEDSIDE

Impact of fragmented QRS complexes on clinical diagnosis of cardiac involvements and prognosis in patients with sarcoidosis

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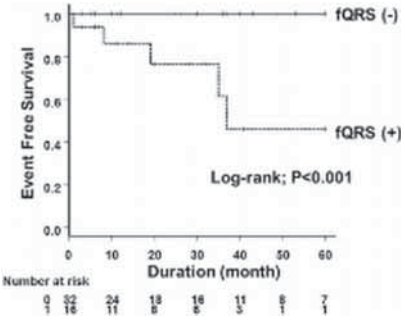
Background: Fragmented QRS (fQRS), defined as the presence of unexpected deviations in the QRS morphology on the 12-lead ECG, has been shown to predict cardiac events in several populations. However, few data exists regarding diagnostic and prognostic utilities of fQRS in patients with sarcoidosis.
Purpose: We investigated whether fQRS can be used to diagnose cardiac involvements and also to predict the occurrence of cardiac events in patients with sacoidosis.
Methods and results: Consecutive 48 patients diagnosed with cardiac (n=19) or extra-cardiac sarcoidosis (n=29) were enrolled in this study. Cardiac events included cardiovascular death, hospitalization due to heart failure, symptomatic atrioventricular block, and ventricular tachyarrhythmia. fQRS was observed in 10 (52.6%) of 19 patients with cardiac sarcoidosis while only 6 (23.1%) of 29 patients with extra-cardiac sarcoidosis exhibited fQRS (p=0.031). Logistic regression analysis revealed that fQRS was an independent and only electrocardiographic predictor for the presence of cardiac involvements (odds ratio, 4.71; 95% confidential interval, 1.18-18.8; p=0.0287). Kaplan-Meier survival curves for cardiac events in all 48 patients demonstrated a significantly higher incidence of cardiac events in patients with fQRS (n=15) compared to those without fQRS (n=33) (log-rank; p<0.001)



Kaplan-Meier survival curve.

Conclusion: These findings suggest that fQRS may be useful in diagnosis of cardiac sarcoidosis. Further, fQRS may predict the occurrence of cardiac events in patients with carvoidosis. Even in the availability of specialized cardiac imaging techniques such as cardiac magnetic resonance or positron emission tomography, fQRS on 12-lead ECG can be a simple and cost-effective tool in diagnosis and risk stratification of patients with sarcoidosis.

P5263 | BEDSIDE

Regional distribution of T-wave alternans in patients with genotyped long QT syndromes assessed by 24-hour 12-lead electrocardiography: What is the optimum lead?

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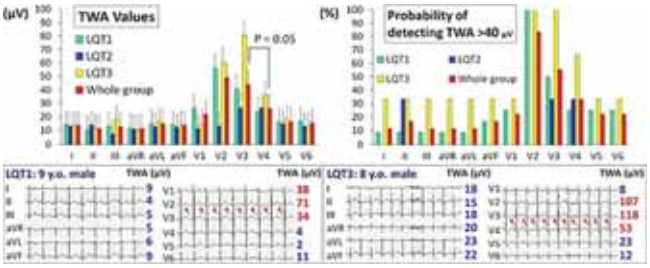
Purpose: To elucidate the optimal electrocardiogram (ECG) lead for detecting T-wave alternans (TWA) in patients with genotyped long QT (LQT) syndromes using 12-lead continuous ECG monitoring.
Methods: 24-h 12-lead ECG was recorded in 23 patients (10 male; mean age, 13.8±7.9 years) with congenital LQT syndrome types 1 (LQT1, n=15), 2 (LQT2, n=4), and 3 (LQT3, n=4). Peak TWA was determined by the modified moving average method. TWA in the other 11 leads at the time of peak TWA was also

measured. The lead with the peak TWA values in each patient was termed the "highest lead". The probability of detecting TWA >40 μV was evaluated in each of the 12 leads.

Results: TWA >40 μV was recorded in 78.3% (18/23) of the patients (12/15 in LQT1, 3/4 in LQT2, 3/4 in LQT3). In the whole group, mean TWA was highest in lead V2 (49.1±28.6 μV) and the second highest in lead V3 (43.7±31.0 μV), which was significantly higher than in the third highest lead V4 (26.1±27.4 μV) (P=0.05). The highest lead was V2 in 9 patients (all LQT1), V3 in 9 patients (4 LQT1, 1 LQT2 and 4 LQT3), V4 in 3 patients (1 LQT1 and 2 LQT2), and II in 2 patients (1 LQT1 and 1 LQT2). The probability of detecting TWA >40 μV was the highest in lead V2 (83.3%). The precordial leads V2-4 could detect 94.4% of the episodes of TWA >40 μV.



Figures

Conclusions: TWA is regionally specific and more prevalent in the precordial leads, particularly in V2 and 3, in LQT patients. Thus, use of limited ECG leads may lead to underestimation of TWA, which is not only one of the diagnostic criteria for LQT syndrome but also a risk marker for lethal cardiac arrhythmias. The high prevalence of TWA in the precordial leads may provide insights into mechanisms.

P5264 | BEDSIDE
The response of the QT interval to standing in children with long QT syndrome

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Background and aims: Patients with Long QT Syndrome (LQTS) often display paradoxical prolongation of the QT interval in response to an increase in heart rate. Studies in adults have shown that the tachycardia induced by standing can be a useful aid in the investigation and diagnosis of LQTS. However, data on the response of the QT interval to standing in the paediatric LTQS population are limited. This study, therefore, aimed to observe the changes in the QT interval invoked by the action of standing in children with LQTS.

Methods: 48 consecutive children from 45 families with LQTS (aged <18 years; median 13.2 years [interquartile range 8.5-15.1]; 49% female), followed up in a specialist referral centre for paediatric inherited cardiovascular disease underwent supine 12-lead ECG followed by a second ECG immediately after standing. Corrected QT interval (QTc) was measured in lead II using Bazett's and Fridericia's formula. 29 patients from 26 families (60%) had undergone genetic testing (LQT1 n=9, 31%; LQT2 n=5, 17%, LQT3 n=1, 4%, variants of uncertain significance n=5, 17%).

Results: The corrected QT interval (QTc) was 432ms supine vs. 454ms standing (mean increase of 20ms [±50ms]) in lead II. When subdivided by genotype, impairment of the QT response was most pronounced in LQT1 (416ms supine vs. 477ms standing; mean increase of 42ms [±62ms]) compared to LQT2 patients who showed appropriate QTc shortening (468ms supine vs. 432ms standing; mean decrease 35ms [±19ms] p=0.002 compared to LQT2 patients). In patients with a diagnosis of LQTS but a normal QTc at rest, QTc was 407ms supine vs. 443ms standing (mean increase of 35ms [±49ms]).

Conclusions: This study shows that the QTc increases in children with LQTS on standing, particularly in children with LQT1. This may improve diagnostic accuracy in children in whom a diagnosis of LQTS is suspected.

P5265 | BEDSIDE
A novel new magnetocardiography-based algorithm for discrimination between ventricular arrhythmias originating from right ventricular outflow tract and aortic sinus cusp

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Background: Radiofrequency (RF) catheter ablation has been established as an effective and curative therapy for ventricular arrhythmia originating from the outflow tract (OT-VA) in structurally normal hearts.Although there are several reports concerning characteristic 12-lead ECG findings of outflow tract ventricular arrhythmias (OT-VAs), accuracy of the ECG algorisms to predict their origin is sometimes limited. The aim of this study was to develop a magnetocardiography (MCG)-based algorism using a novel adaptive spatial filter to differentiate VA from aortic sinus cusp (ASC-VA) from VA from right ventricular OT (RVOT-VA).

Methods: This study consisted of 51 patients (20 men, mean age 49±15 years) who underwent successful catheter ablation for symptomatic idiopathic VT or PVCs originated from the outflow tracts. Activation mapping and pace mapping were performed during the clinical arrhythmia. In all patients, surface 12-lead ECGs were recorded during sinus rhythm and during the clinical arrhythmia. Transition zone index is defined as TZ score of VA minus TZ score of sinus beat, where TZ score is graded in 0.5-point increments according to the site of the transition zone in the precordial leads.All patients underwent an MCG during sinus rhythm 1 day before ablation. MCG methodology was described in detail previously. An algorithm was developed by correlating the MCG findings with the successful ablation site. The arrhythmias were classified as RVOT-VA or ASC-VA. The following 3 parameters were obtained from 3-D MCG imaging: 1) depth of the origin of OT-VA in the anteroposterior direction, 2) distance between the earliest atrial activation site, i.e., sinus node, and the origin of OT-VA, and 3) orientation of VA propagation at the QRS peak.

Results: The origins of VAs were identified in the RVOT (n=41, 80%) or the ASC (n=10, 20%). There were no significant differences with regard to baseline patient characteristics. ROC analyses determined that depth of origin was the most powerful predictor, with sensitivity of 90% and specificity of 73% (p<0.01, AUC=0.90). Distance between the earliest atrial activation site and angle/vector of arrhythmia propagation showed sensitivity of 90% and specificity of 78% (p<0.01, AUC=0.88) and sensitivity of 80% and specificity of 59% (p=0.03, AUC=0.73), respectively. Discriminant analysis that combined all 3 parameters revealed the accuracy of the localization of 94%.

Conclusion: This new novel MCG-based algorithm using an adaptive spatial filter could precisely discriminate ASV-VAs from RVOT-VAs.

P5266 | BEDSIDE
Arginine-vasopressin system activation and vasoconstriction in vasovagal syncope

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Purpose: The arginine-vasopressin (AVP) system is one of the main pressure regulating systems. Copeptin is a stable and sensitive surrogate marker for AVP release. Copeptin has been found to increase following vasovagal syncope (VVS). However, the pathophysiologic significance of this finding is poorly understood, since VVS is characterized by 2 different patterns of vasoconstrictive adaptation to orthostasis during head-up tilt test (HUT), one which is insufficient ("impaired") and another one, characterized by vasocontristion instability. Purpose of this study was to assess whether different increases in copeptin are observed in these 2 distinct groups of patients (pts) with VVS.

Methods: We studied 36 pts with typical history of recurrent VVS (at least 2 episodes during the preceding 6 months), without underlying heart disease or renal dysfunction, mean aged 51±5 years, 16 males/20 females, who underwent a diagnostic, positive HUT, discontinued at the presyncopal phase of the reflex. They were tilted at 60° for up to 20 min without drug provocation, followed by 0.4 mg of sublingual glyceryl trinitrate (GTN) and HUT continuation for a further 10-min period. Forearm vasoconstriction during the subsequently positive HUT was assessed by changes in forearm blood flow (FBF), as measured by venous occlusion plethysmography, every 15 secs during the 3 mins preceding upright tilt and the first 10 mins of orthostasis; pts were divided in 2 groups, of either impaired vasoconstriction during HUT (<10% reduction in forearm blood flow relative to supine values, FBF, Group A) or unstable vasoconstriction (>20% changes in the initial upright values, Group B) relative to controls (n=18), who also underwent a similar HUT.

Results: Baseline copeptin values were similar in the 2 groups of pts and controls (9.3±5.6 pmol/l and 8.5±5.1 pmol/l in pts vs 7.9±3.6 pmol/l in controls, p: NS). A significant difference was observed in copeptin values between the 2 patient groups following HUT termination and controls (45.3±10.5 in the impaired response type vs 80.2±45 in the unstable type vs 13.6±9.4 in controls, p<0.05 between the 2 patient groups as well as between each patient group and controls).

Conclusion: In pts with VVS and a positive HUT, copeptin values are increased, especially in those with unstable vasoconstriction prior to presyncope. These findings imply that the AVP secretion axis is activated prior to a positive response, possibly in an attempt to counterbalance a (still not well understood) defect in adaptation to orthostasis, characterized by unstable vasoconstriction during HUT.

P5267 | BEDSIDE
Autonomic dysfunction patients with J wave

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Background: The potential arrhythmogenicity of J wave syndrome has recently thought to be associated with the autonomic abnormality in some experimental models. However, clinical supporting evidence is lacking. The aim of this study

was elucidate the relation between the manifestation of early reporalization (ER) patern and J wave and autonomic function using head-up tilt test (HUT).
Methods and results: A total of 191 patients (49.9±21.4 years) underwent HUT using 12-leads electrocardiogram (ECG) and impedance cardiography. If patients didn't show syncope or presyncope, HUT was repeated under drug loading (adenosine triphosphate, isosorbide dinitrate, isoproterenol).
At baseline ECG, 17 patients showed ER pattern with J point elevation (>1mm) (ER group) (35.4±21.5 years), 24 showed J wave, notch or slur of the terminal of the QRS (J group) (51.2±24.0 years) and 17 showed J wave with ER pattern, (J-ER group) (36.9±17.7 years) at least in 2 leads of inferior (II, III, aVF) or lateral (I, V4-6) leads. 133 patients didn't show any remarkable change which suggests idiopathic ventricular fibrillation (N-group).
Patients in J and J-ER groups showed high positive rate of HUT compared to that in N and ER-groups (31/42 vs. 56/149, P<0.01). The appearance of J wave was frequently observed in inferior leads compared to lateral leads (36 vs. 12).
Conclusions: Our findings suggest that abnormal autonomic nerve activity is a factor of the manifestation of J wave especially in inferior leads and may link to arrhythmogenicity of J wave syndrome.

P5268 | SPOTLIGHT
Prognostic analysis of heart rate variability assessment in familial amyloid polyneuropathy

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Introduction: Familial amyloid polyneuropathy (FAP) V30M-TTR, a rare form of hereditary amyloidosis, is characterized by progressive autonomic neuropathy. The disease is associated with conduction disturbances, increased risk of complications during anesthesia and, in rare cases, sudden death. These events are attributed to autonomic dysfunction. The heart rate variability (HRV) which integrates the balance of sympathetic and parasympathetic tone may be a useful tool for prognostic stratification in these patients.
Aim: To study the prognostic value of heart rate variability analysis assessed by 24 hr Holter monitoring in FAP.
Methods: Prospective observational study of consecutive patients with V30M-TTR mutation. All patients were evaluated annually and underwent 24h Holter monitoring. To evaluate the predictive value of the mean heart rate (HR), PNN-50, PNN-30, RMSSD, SDNN, Total Power, VLF, LF, HF and LF-HF ratio in the risk of death, from any cause, multivariate Cox regression analysis with adjustment for age and Kaplan-Meier survival analysis were used.
Results: 223 patients (mean age of 44±14 years; 54.3% female) were included. During a median follow-up of 55 months, 777 Holter exams were performed. From a total of 635 exams in sinus rhythm, time and frequency domain analyses of heart rate variability were available in 575 exams. The independent predictors of prognosis were age, mean HR and VLF. The risk of death increased with age (HR: 1.054; IC 95% 1.026-1.083; P<0.001) and varied inversely with the mean HR (HR: 0.936; IC 95% 0.905-0.968; P<0.001) and VLF (HR: 0.420; IC 95% 0.244-0.723; P=0.002). The risk of mortality differed significantly according to the tertiles distribution of these variables, being twice in patients with VLF <279 ms2 (HR: 2.16; IC95% 1.20-3.87; P=0.010) and 9 times higher in patients with mean HR <75bpm (HR: 9.39; IC95% 4.70-18.77; P<0.001).
Conclusion: Very Low Frequency and mean HR assessed by 24 hr Holter monitoring are independent predictors of prognosis in patients with FAP V30M-TTR.

P5269 | BEDSIDE
Athletes with prolonged QT interval: is QT hysteresis analysis a useful method to distinguish healthy athletes from LQTS patients?

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Purpose: Competitive athletes have often a prolonged QT interval. Currently, genetic test is used to distinguish healthy athletes from LQT1/LQT2 patients, but it is expensive, it takes long timeline and it is negative in about 30% of cases with clinical diagnosis of long QT Syndrome. Aim of the study was to evaluate whether the trend of QT hysteresis could be used as a new diagnostic method to distinguish healthy athletes from LQTS subjects and to hypothesize the involved gene (LQT1, LQT2).
Methods: Four groups of subjects were created. LQT1: 6 subjects (mean age 24±13 years) with prolonged QT interval at rest ECG (QT: 510±67 ms) and positive genotype (KCNQ1 mutation). LQT2: 5 subjects (mean age 20±3 years) with prolonged QT interval (QT: 490±56 ms) and positive genotype (KCNH2 mutation). ATHLETES (ATH): 6 competitive sport athletes (mean age 15±3 years) sent from the Sport Medicine Institute for further investigations after the recognition of a prolonged QT interval at basal ECG (QT: 480±52 ms) or during exercise test; all of them had negative genotype. Any group was compared with a control group (CTRL) with normal QT interval at resting ECG: CTRL-LQT1/2 consisted of 19 subjects (mean age 18±5 years); CTRL-ATH consisted of 16 athletes (mean age 16±3 years). All subjects underwent treadmill exercise test according to Bruce protocol. Hysteresis was calculated subtracting the QT interval measured at 80, 100 and 120 bpm during exercise from the QT interval at the same heart rate (HR) into the recovery phase. QT and QTc values were expressed as mean ± standard deviation and compared using Student's t test.
Results: In LQT1 group the QT hysteresis resulted significantly greater compared to CTRL group at all HR considered (p<0.001 at 80, 100 and 120 bpm). Also in LQT2 group the QT hysteresis was significantly different from that of the CTRL (p<0.001 at all the HR considered). There was also a significant difference in QT hysteresis between LQT1 and LQT2 groups at all HR considered (p<0.01). Moreover QT hysteresis in the LQT2 group had a positive value differently from all the other groups, in which it was negative. In ATH group QT hysteresis behaviour was similar to the CTRL group (p=NS at all the HR considered). The QT hysteresis was significantly different between LQT1 and ATH group at 100 and 120 bpm (p=0.05 and p=0.02). It was also different between LQT2 and ATH group at all the HR considered (p<0.03).
Conclusions: Our results show that QT hysteresis analysis allows to distinguish healthy athletes with prolonged QT interval from patients with LQT syndrome and LQT1 from LQT2 patients.

P5270 | BEDSIDE
Maximal T-wave alternans site in 12-lead holter ECG correlates with distribution of late gadolinium enhancement on cardiac MRI in nonischemic cardiomyopathy

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Background: The distribution of late gadolinium enhancement (LGE) on cardiac MRI (CMR) represents myocardial scar producing abnormal repolarization and depolarization. T-wave alternans (TWA) is a potent cardiac mortality predictor in patients with nonischemic cardiomyopathy (NICM). However, whether LGE distribution affects TWA is unclear. [Purpose]: To elucidate the relationship between the LGE distribution and maximal TWA lead (TWAmax-lead) location and maximal TWA voltage (TWAmax) assessed with 12-lead Holter ECGs in NICM.
Methods: 12-lead Holter ECGs and CMR were performed in 30 NICM patients. TWA was assessed by a modified moving average method and TWAmax was determined at heart rates<120bpm in each lead. In addition, we defined TWA dispersion (TWAd) as [TWAmax – minimal TWA] of the 12-leads in each patient. The average transmural LGE extent was scored as 4 points in 12 left ventricular segments, and the sum (LGEtotal) was calculated. Left ventricular LGE sites were classified into anterior, septal, inferior and lateral. The corresponding ECG lead groups were defined as V3-4 for anterior, V1-2 for septal, II, III and aVF for inferior and I, aVL, and V5-6 for lateral. The coincidence between the LGE distribution and TWAmax-lead, and correlation between the LGEtotal and TWAmax were investigated. The differences in the LGEtotal, TWAmax, and TWAd in the presence or absence of ventricular tachycardia (VT) were also studied.
Results: The LGEtotal positively correlated with the TWAmax (r=0.59, p=0.004). In LGE positive cases, the TWAmax-lead revealed LGE scores ranging from 2 to 3 in all segments, and the rate of the segments adjacent to the highest LGE coinciding with the TWAmax-lead was 22/26 (85%). Furthermore, the LGEtotal, TWAmax, and TWAd were significantly greater in those with VT (n=15) than without (18.8±5.8 vs. 11.4±7.7 [p=0.018], 86.1±17.9μV vs. 68.2±14.9μV [p=0.021], 55.5±21.3μV vs. 31.2±10.9μV [p=0.004], respectively).
Conclusions: The LGE distribution correlated with TWA, i.e., LGE transmurality yields the maximal TWA on the corresponding lead in the vicinity of scar. The spatial distribution of LGE strongly affects myocardial repolarization abnormalities indicated by TWA as VT substrates in NICM.

P5271 | BEDSIDE
Investigation of the interaction between a novel electrical restitution based sudden cardiac death biomarker and autonomic function

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Purpose: The Regional Restitution Instability Index (R2I2) is a promising new ECG based biomarker of sudden cardiac death (SCD). R2I2 quantifies heterogeneities in electrical restitution, which is in turn affected by autonomic function. This study explores this relationship for the first time.
Methods: Blinded prospective observational study of 44 ischaemic cardiomyopathy patients undergoing risk stratification for implantable cardioverter defibrillator. The R2I2 technique has been described previously: an EP study is performed and ECG surrogates for action potential duration and diastolic interval are used to measure restitution heterogeneity. Patients underwent 24-hour ambulatory ECG monitoring and heart rate variability was quantified by calculating the triangular index.
Results: During median follow up of 22 months, 11 patients experienced ventric-

ular arrhythmia (VA)/SCD. R2I2 was significantly higher in patients experiencing VA/SCD than those not (mean±SEM: 1.14±0.11 vs 0.84±0.05 p=0.01). R2I2 was independent of HRV-i and LVEF in prediction of endpoint (Cox model, p=0.002). Weak negative correlation was seen between R2I2 and HRV-i (Figure 1). Patients with low HRV-i (<20) experienced a higher rate of VA/SCD than those with high HRV-i (42% vs. 19%, p=0.12). Patients with R2I2≥1.03 and HRV-i<20 had a hazard ratio for VA/SCD 7.8 times that of patients negative for both (Cox model, p<0.003).

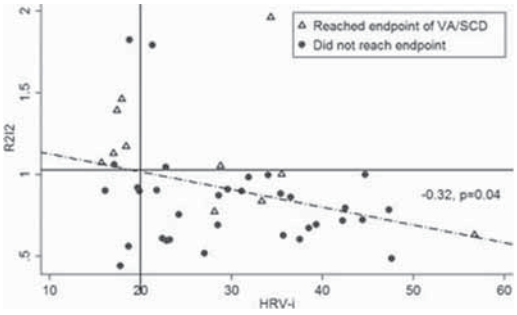

Figure 1. R2I2/HRV-i scatter plot.

Conclusions: A weak tendency to higher R2I2 values in patients with autonomic dysfunction is seen. Combining R2I2 with HRV-i may improve its performance as an SCD risk marker. These data begin to answer the challenge that R2I2 is a quantification of autonomic dysfunction and raise the possibility that R2I2 could be effective in populations with normal autonomic function.

P5272 | BEDSIDE
Prevalence of type 1 Brugada electrocardiographic pattern evaluated on 12-lead 24-hour Holter monitoring

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Purpose: The presence of spontaneous type 1 ECG pattern (BrECG) is considered a risk factor in Brugada syndrome, although it could be underestimated because of the well-known BrECG fluctuations. Aim of the study was to analyse in a large population of Brugada patients the prevalence of type 1 BrECG using 12-lead 24-hour Holter monitoring (12L-Holter) and to evaluate its reproducibility and correlation with the time of the day.
Methods: We collected 234 12L-Holter recorded in 187 patients from the 679 of the Brugada Registry of a region of Italy. Thirty-six patients (19%) had from 2 to 3 12L-Holter. Among the patients included in the study, 67 (36%) exhibited spontaneous type 1 BrECG in at least one 12-lead ECG recorded before 12L-Holter, while 120 (64%) had only drug-induced type 1 BrECG. Twenty-four (13%) were symptomatic for syncope, 1 had aborted sudden death and 162 (86%) were asymptomatic. 12L-Holter were recorded in the right precordial leads both at 4th and 2rd intercostal space and were analysed independently by two cardiologists. In order to evaluate the circadian fluctuations of the BrECG, 4 periods were considered: 12 midnight-6 am, 6 am–12 noon, 12 noon-6 pm and 6 pm-12 midnight. The burden of type 1 BrECG was defined as "permanent" (>85% of the 12L-Holter recording), "intermittent" (between 60 seconds and 85% of the recording), "absent" (less than 60 seconds).
Results: Twenty-three (19%) out of 120 patients with drug-induced type 1 BrECG, developed intermittent spontaneous type 1 BrECG in at least one 12L-Holter. Forty (59%) out of 67 patients with previously documented spontaneous type 1 BrECG on 12L-ECG showed intermittent type 1 in at least one 12L-Holter, 9 (13%) had persistent type 1 in all the 12L-Holter; 18 (27%) never had spontaneous type 1 at 12L-Holter: in 5 of them the type 1 BrECG had been documented only during fever. Spontaneous type 1 BrECG on 12L-Holter was present in 56% of symptomatic and 47% of asymptomatic patients (p=NS) and was most frequently recorded between 12-noon and 12-midnight (85%) than between 12 midnight and 12 noon (15%, p<0.001). Nine out of the 36 patients (25%) with more than one 12L-Holter showed discordant results concerning the presence of spontaneous type 1.
Conclusions: 12L-Holter recording significantly increases the chances to identify spontaneous type 1 BrECG. Significant fluctuation of BrECG pattern is also present in serial 12L-Holter recordings. Type 1 BrECG was mainly documented between 12 noon–12 midnight. Further studies are needed to establish the correlation between spontaneous type 1 BrECG and ventricular arrhythmic events.

BASIC ADVANCES IN ATRIAL FIBRILLATION

P5274 | BENCH
Inhibitory effects of prednisolone on the recurrence after atrial fibrillation ablation in a rat model

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Background: We previously reported that transient use of corticosteroids after atrial fibrillation (AF) ablation was effective for preventing AF recurrences. However, the mechanism underlying the suppressive effect of corticosteroids on AF recurrences has not been fully examined.
Methods: Ten-week-old-Wister rats were divided into 3 groups: ablation (A)-group, ablation and steroid (AS)-group, and control (C)-group. Rats in A- and AS-groups underwent right atrial linear ablation with a 2-French transvenous catheter, and rats in C-group underwent catheter insertion without ablation. Rats in AS-group were treated with prednisolone (10mg/kg/day) intragastrically, and rats in A- and C-groups were treated with vehicle from 5 days before the procedure. One week after the procedure, the durations of AF induced by 30-second burst pacing were measured. Atrial structural changes were assessed histologically, and tissue levels of inflammatory cytokines in the atria were measured by multiplex immunoassay.
Results: AF duration was significantly shorten by ablation, and additionally reduced by prednisolone (19.0±5.8s[C-group], 10.3±5.0s[A-group] vs. 4.8±3.9s[AS-group]). Microscopic analysis revealed suppression of ablation-related histological changes (inflammatory cell infiltration and interstitial fibrosis) by prednisolone. The tissue levels of TNF-α, MCP-1, IL-17A, IL-18, and VEGF were significantly enhanced by ablation, and were significantly reduced by prednisolone (Table).

	Tissue levels of inflammatory cytokines in the atria (pg/1mg protein)			p value	
	(C)-group	(A)-group	(AS)-group	(C) vs. (A)	(A) vs. (AS)
TNF-α	22.5±6.6	34.3±15.4	22.9±5.6	0.039	0.047
MCP-1	1453±429	2178±668	1588±222	0.006	0.026
IL-17A	100±37	184±94	110±18	0.010	0.024
IL-18	9122±2134	15481±4923	10806±1160	<0.001	0.007
VEGF	845±274	1991±1575	885±226	0.028	0.034

Conclusions: Prednisolone enhanced the efficacy of AF ablation by suppressing several kinds of inflammatory cytokines and inhibiting histological changes in the ablated lesions.

P5275 | BENCH
A renin inhibitor prevents atrial endocardial dysfunction in rapidly paced rats with streptozotocin-induced diabetes

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Objectives: Thrombogenesis in atrial fibrillation (AF) is related not only to abnormal blood flow but also to abnormal composition of blood and atrial endocardial dysfunction. AF per se causes atrial endocardial dysfunction leading to local coagulation imbalance on the internal surface of the atrium, which contributes to thrombus formation in the fibrillating left atrium. On the other hand, diabetes mellitus (DM), which is associated with an increased incidence of AF, and AF both independently increase serious stroke. However, it is unknown whether a renin inhibitor has beneficial effect on atrial endocardial dysfunction by AF or DM. Therefore, we assessed whether a renin inhibitor, aliskiren, ameliorates atrial endocardial dysfunction in rapidly paced rats with DM.
Methods: Wild and diabetic Sprague-Dawley rats were treated with valsartan (30 mg/kg, orally) or aliskiren (30 mg/kg, orally) for two weeks prior to the rapid pacing. These medications began 48 h after streptozocin injection in diabetic rats. Then, we examined the effects of valsartan and aliskiren on the expression of tissue factor pathway inhibitor (TFPI), thrombomodulin (TM), and plasminogen inhibitor-1 (PAI-1) in the endocardium of the rapidly paced rat atria by means of immunohistochemistry and western blotting.
Results: Rapid pacing induced a significant decrease in TFPI, TM and an increase in PAI-1 protein in the left atrium in both wild and DM rats. Pre-administration of valsartan and aliskiren significantly prevented the down-regulation of TFPI, TM and attenuated the up-regulation of PAI-1 in wild rats. Furthermore, aliskiren but not valsartan prevented these changes in rats with DM.
Conclusions: A renin inhibitor, aliskiren, could prevent the atrial endocardial dysfunction by rapid atrial pacing in diabetic rats. This data suggest the potential usefulness of aliskiren as a new therapeutic basis for stroke prevention in AF, in particular, complicated with DM.

P5276 | BENCH
Functional characterization of novel PITX2 homeodomain mutations in AF patients

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Atrial fibrillation (AF) is the most common cardiac arrhythmia in the human population, with an estimated incidence of 1-2% in young adults but increasing to more that 10% in 80+ years patients. Albeit AF is a frequent electrophysiological disorder, to date, the genetic bases of AF remain rather elusive. Point mutations in a large variety of ion channels have been described in familial cases of AF, yet explaining a minority of cases. Recently, genome wide association studies (GWAS) have unraveled risk SNPs highly associated with AF, among which the most significant are located in 4q25 locus. Surprisingly these risk alleles are located in a gene desert, being the closest gene PITX2. Experimental evidences of Pitx2 loss-of-function in mice revealed that this homeodomain (HD)-containing transcription factors plays a pivotal role in atrial electrophysiology. Therefore these data, underscore PITX2 as a candidate gene for AF. In this context, we have recruited 31 AF patients from the Regional Hospital "Ciudad de Jaén" for genetic analyses of both the risk alleles and PITX2 ORF re-sequencing. Among those patients, we have found two point mutations in the HD of PITX2 and three other mutations in the 5'untranslated region. A 65 years male patient with recurrent AF displayed two distinct HD-mutations, G947A (Q103H) and G1008A (E124Q), which both resulted in a change within a highly conserved amino acid position. Curiously, no 4q25 risk variants were present in this subject. Both PITX2 HD mutations were further followed for functional studies. We generated plasmid constructs with mutated version of each nucleotide variant (MD4 and MD5, respectively) as well as a dominant negative control construct in which the PITX2 HD was lacking (DN). Functional analyses demonstrated PITX2 MD4 and PITX2 MD5 decreased Nppa-luciferase transactivation by 50% and 40%, respectively, in a similar range as PITX2 DN (50%). Co-transactivation with other cardiac-enriched transcription factors, such as Gata4 and Nkx2.5, was similarly impaired, further supporting the pivotal role of these mutations for correct PITX2 function. We are currently evaluating the functional consequence of these mutations in a cardiomyocyte context. Preliminary data suggest that distinct AF-related genes are similarly impaired. In summary, we have identified novel PITX2 mutations in an AF patient, which functionally impairs the transactivating capacity of PITX2.

P5277 | BENCH
Dose dependent pitx2 loss of function impairs zfhx3, wnt8a and calcium handling; novel links to atrial arrhythmogenesis

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Atrial fibrillation (AF) is the most common cause of arrhythmogenesis in humans yet the genetic cause of AF remains elusive. Recent genome-wide association studies (GWAS) have reported risk variants in four distinct genetic loci (4q25, 1q21, 16q22 and 16q13) which have been associated with AF. Among them, the most significant are 4q25 risk variants, which are located in the vicinity of the PITX2 gene. Given the key developmental role of Pitx2 during cardiogenesis and particularly its role in pulmonary vein deployment, it has been postulated that Pitx2 dysfunction might be the molecular link to AF.
Experimental evidences in distinct laboratories, including ours, have demonstrated that Pitx2 loss of function predisposes to atrial arrhythmogenesis. However, the molecular mechanisms driven by Pitx2 in this context remain somehow elusive, proposing either embryonic or mature gene expression defects. In order to get further insights into the molecular mechanisms driven by Pitx2 and their putative relation with novel AF GWAS associated genes, we have generated a new Pitx2 conditional mouse line, by intercrossing Sox2Cre and Pitx2floxed mice. Epiblast deletion of Pitx2 leads to the generation of heterozygous and systemic null Pitx2 null mutants, respectively. As expected, embryonic mortality and cardiac defects were similarly observed in Sox2CrePitx2 null mice as those previously reported for Pitx2 knock-out mice. Molecular analyses of the left atrial appendage in heterozygous Sox2CrePitx2 mice (20-30% reduction in Pitx2 expression) and atrial-specific NppaCrePitx2 null mice (60-70% reduction in Pitx2 expression) demonstrate that AF GWAS associated genes such as Zfhx3, Kcnn3 and Wnt8a are severely impaired while other such as Cav1, Synpo2l or Prrx1 are not. Surprisingly, beta-adrenergic signaling is not altered in these models whereas multiple calcium handling genes such as Serca2a, calsequestrin, phospholamban are severely impaired in atrial-specific NppaCrePitx2 null mice but not in heterozygous Sox2CrePitx2 mice. Functional assessment of calcium handling further underscores these findings. Importantly, neither Zfhx3 nor Wnt8a gain-of-function or loss-of-function experiments impairs Pitx2 expression, suggesting that Pitx2 is upstream of these genes. Furthermore, these data suggest a dose–dependent relation between Pitx2 expression and the susceptibility to display basal or only inducible electrophysiological defects. We are currently studying the hierarchical between Pitx2, AF GWAS associated genes and calcium handling, as well as to putative involvement of post-transcriptional modulators such as microRNAs.

P5278

P5279 | BENCH
Atrial fibrillation coincides with increased intravascular depositions of the advanced glycation end-product n-epsilon-(carboxymethyl)lysine in the atria of the heart

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Purpose: The pathophysiology of atrium fibrillation (AF) is associated with inflammation. In the blood of AF patients, increased plasma levels of the advanced glycation end product (AGE) Nε-(carboxymethyl)lysine (CML) have been described. It is known that presence of AGEs can induce a proinflammatory phenotype in the (micro)vasculature in patients with AF. Albeit, the formation of AGE's within atrial tissue is unknown. This we have now analysed in atrial tissue of patients with idiopathic AF.
Methods: Left atrial tissue were obtained at surgery from 35 patients with idiopathic AF and at autopsy from 7 control patients. These specimen were quantatively analysed via immunohistochemistry for the presence of CML, VCAM-1, neutrophilic granulocytes, lymphocytes and macrophages. These stainings were quantified in the epicardium and myocardium of the atria separately.
Results: A significantly increased presence of CML was found in blood vessels of the left atrium in patients with AF compared to controls. Furthermore, significantly increased expression of VCAM-1 in blood vessels and a significant increase in the number of infiltrated neutrophilic granulocytes, lymphocytes and macrophages were found in the left atrium of AF patients compared to controls. Interestingly, the numbers of CML-positive bloodvessels, VCAM-1 positive bloodvessels and infiltrating inflammatory cells, were found to be higher in the epicardium compared to the myocardium. Finally, the CML formation found in the blood vessels in the left atrium of patients with AF correlated positively with the increased numbers of macrophages.
Conclusions: Our findings indicate that in idiopathic AF the intramyocardial arteries of the left atrium have a pro-inflammatory status coinciding with a local increase in the number of neutrophilic granulocytes, lymphocytes and macrophages.

P5280 | BENCH
Prothrombotic potential of galphaq signalling in the left atrium

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Heterotrimeric G proteins are membrane-associated proteins that comprise an alpha, beta and gamma subunit and are the intracellular mediators of G-Protein coupled receptor activation (Park et al., 2004; Neer et al., 1994; Salazar et al., 2001). Transgenic overexpression of constitutively active Gαq under the control of the alpha myosin heavy chain promoter leads to cardiac hypertrophy, re-expression of foetal genes, diffuse atrial and ventricular fibrosis, atrial fibrillation and ultimately heart failure (Mende et al., 1998, Hirose et al., 2009).
Echocardiographic analysis revealed increased atrial size and reduced atrial function in 16 week old Gαq mice prior to the development of compromised ventricular function. Atrial thrombi were found in 33% of Gαq mice at 16 wks of age (n=69), but no thrombi were observed in wild type controls (n=43) ($p<0.05$). Telemetric electrocardiogram recordings (n=6, 15-17 hours recording/mouse) identified very short episodes of paroxysmal AF (on average 32 sec per day) in Gαq mice >12 weeks old (5 out of 6 mice). In addition, we found atrial thrombi in 14% of mice without documented AF (n=43), suggesting that enhanced activation of Gαq signalling may have a direct prothrombotic effect on atrial cardiac tissue.
We therefore analysed atrial gene expression in search for prothrombotic genes. A Mind Map of prothrombotic proteins that may act downstream of Gαq signalling was compiled by combining DAVID (Database for Annotation, Visualization and Integrated Discovery) and IPA (Ingenuity Pathway Analysis) analyses of an RNA-seq dataset generated from whole heart from a second transgenic mouse line overexpressing Gαq protein (Matkovich et al., 2010). Prothrombotic candidates identified via literature search and linked to Gαq were also included in the Mind Map. The expression levels of 20 candidate genes were quantified in the left atria (LA) of 8-14 wk old mice (n=7-15 transgenic and n=9-18 wild type) by RT-PCR.
Four candidate genes were found to be significantly upregulated in Gαq LA compared to wild type LA: Tenascin C (TnC, 3.3 fold, $p<0.001$); von Willebrand Factor (1.7 fold, p=0.006); Thrombospondin 1 (2.2 fold, p=0.03) and Serpin peptidase inhibitor, clade E1 (2.6 fold, p=0.01). Ongoing quantification of the protein products encoded by the aforementioned genes has thus far supported upregulation of TnC in Gαq atria (1.4 fold for protein, p=0.02).
Together, these results support the upregulation of prothrombotic transcripts and protein products in left atria of the constitutively active Gαq transgenic mouse, indicative of Gαq signalling promoting a prothrombotic environment.

P5281 | BENCH
Inhibition of aldosteronsynthase CYP11B2 inhibits atrial fibrosis during atrial fibrillation in vivo and in vitro

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Introduction: Earlier studies have suggested that inhibition of aldosterone-synthase CYP11B2 may reduce fibrosis in the left ventricle. The role of CYP11B2 inhibition for structural remodeling during atrial fibrillation (AF) is unknown.
Methods and results: Primary neonatal cardiac fibroblasts were stimulated with angiotensin II (1μM; 3 hours) and pre-incubated with or without the CYP11B2 specific inhibitor SL 242. SL 242 (1μM; 24 hours) reduced the expression of the pro-fibrotic cytokine connective tissue growth factor (CTGF), the key enzyme of collagen crosslinking lysyl-oxidase (LOX) and the fibrosis regulator microRNA-21 (miR-21) as well as the collagen content, whereas Rac1 expression and activity was unaffected. Lung fibroblastes (V97MZ cells) deficient of endogenous aldosteronsynthase were transfected with human aldosteronsynthase (CYP11B2) and treated with torasemide. These experiments showed that torasemid inhibited CYP11B2 activity by 75±1.8%, most likely through a competitive inhibition of CYP11B2 by binding of torsemide to the heme binding site of CYP11B2 through its nitrogen ring. Mineralcorticoid receptor expression and activity was not altered by torsemide.
In order to test the effect of CYP11B2 inhibition in vivo, transgenic mice with cardiac overexpression of Rac1 GTPase (RacET) which develop spontaneous AF were treated with torsemide (10mg/kg/day) for 8 months. Untreated RacET are characterized by increased atrial fibrosis, increased protein expression of CTGF (257±77%), LOX (195±24%) and the miR-21 (252±43%) compared to wildtypes (WT). Long-term treatment with torsemide prevented atrial fibrosis in RacET as well as the up-regulation of CTGF (62±18%), LOX (124±23%) and miR-21 (68±7%) compared to vehicle, whereas Rac1 expression and activity remained unaffected. Torsemide did not affect blood pressure but reduced the prevalence of atrial fibrillation (38% RacET+Tora vs. 70% RacET). All effects are significant with $p<0.05$.
Conclusion: Inhibition of aldosteronsynthase (CYP11B2) prevents atrial fibrosis and reduced the prevalence of atrial fibrillation in mice. These effects were mediated through reduced expression of the profibrotic regulators CTGF, LOX and miR-21.

P5282 | BEDSIDE
Relationship between local production of microRNA-328 and atrial substrate remodeling in atrial fibrillation

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Objectives: Recent experimental studies demonstrated the possible roles of micro RNAs (miRs), a new class of non-coding RNAs, in atrial fibrillation (AF). However, no data exist about the relationship between intracardiac plasma level of miRs and the existence of AF or the atrial remodeling. In the present study, we investigated whether the local and systemic levels of miRs might be associated with the existence of AF and the left atrial (LA) substrate properties.
Methods: Bloods from the periphery, pulmonary vein (PV) and left atrial appendage (LAA) were sampled from 28 patients with AF undergoing PV isolation, and from 10 control subjects with WPW syndrome. We measured peripheral, PV and LAA plasma levels of miR-1, -26, -133a, -328, -590, which regulate the genes encoding cardiac ion channels, gap junction proteins, calcium-handling proteins, or profibrotic growth factors, by TaqMan PCR. The LA global contact mapping during sinus rhythm was performed (by NavX system) before PV isolation.
Results: Plasma level of miR-328, which targets CACNA1C and CACNB1 genes (encoding L-type calcium channel subunits), was higher in patients with AF than in control subjects. Plasma miR-328 level was significantly higher in the LAA than the periphery and PV in patients with AF, but not in control subjects. Plasma miR-1 level, which targets GJA1 gene (encoding connexin43) and KCNJ2 gene (encoding inward rectifier potassium channel Kir 2.1), was also higher in the LAA than the PV in AF patients. Patients with AF and control subjects showed no significant differences in levels of miR-26, -133a, and -590 between the periphery, PV and LAA. Interestingly, LAA plasma level of miR-328 showed significant correlation with LA volume and LA voltage zone index (area with voltage <0.5mV divided by total LA surface area). These correlations were stronger than those between miR-328 level in the periphery and LA volume or LA voltage zone index.
Conclusions: These results suggest that local production of miR-328 in LA might be involved in the process of atrial remodeling in patients with AF.

P5283 | BENCH
Atrial fibrillation and rapid acute pacing provoke induction of adipocyte/adipositas-associated gene expression in the atria

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Purpose: Atrial fibrillation (AF) has been associated with increased volumes of epicardial fat and atrial adipocyte infiltration. Mechanisms initiating and promoting atrial adipositas are not well understood. This study aims to identify AF-dependent changes in adipocyte-specific atrial gene expression in both an experimental model of and patients with AF.
Methods: Right atrial (RA) tissue samples and adjacent epicardial adipose tissue (EAT) were obtained from 24 patients; 12 with AF, 12 with sinus rhythm (SR). RA samples were also obtained from 4 pigs subjected to 6 hrs of rapid acute pacing (RAP) plus 4 sham-operated controls (sham). Adipocyte and adipositas associated gene expression was determined by microarray analysis in porcine and by qRT-PCR in human samples. Target genes analysed include adiponectin, resistin, insulin like growth factor (IGF) 1, IGF2, IGF-binding protein (IGFBP) 5 and 6.
Atrial adipositas was determined by sudan III staining in human atrial tissue slices.
Results: In patients with AF as well as after 6 hours of RAP in pigs, there was a comparable significant change in the RA and EAT mRNA expression of resistin (RAP: 2.6-fold; RA: 1.7-fold; EAT: 2.4fold) and IGF1 (0.66-fold; 0.5-fold; 0.55-fold). mRNA levels of adiponectin were increased by RAP (1.46-fold), but were reduced by AF in both RA and EAT (0.55-fold; 0.48-fold).
IGF2 and IGFBP5 were down-regulated in RAP and EAT (0.55-fold; 0.67-fold/0.4-fold; 0.5-fold), but remained unchanged in RA samples from AF. IGFBP6 mRNA levels were doubled by RAP, and reduced about 0.7-fold in EAT.
Sudan III staining revealed a significant increase in lipid/adipocyte contents of atrial tissue from patients with AF, when compared to SR (250±45% of SR).
Conclusions: AF and RAP provoke significant changes in adipositas-associated gene expression in RA and EAT. Although comparable changes could be observed for some target genes (e.g. resistin), there were apparent differences in the tissue responsiveness. These data suggest that AF provokes complex alterations of the local humoral network which (I) depend on the duration of AF (RAP vs. AF patients) and, (II) involves various cell types with their specific production of and responsiveness to these peptide hormones. Consequently, altered

atrial expression of cardiomyocyte- and adipocyte-derived cytokines/growth factors might facilitate atrial adipositas and adipocyte infiltration, thereby promoting and perpetuating the development of an arrhythmogenic substrate.

P5284 | BENCH
Increased frequency of CD4+CD28null T lymphocytes in patients with atrial fibrillation

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Purpose: Despite its easy detection and well-defined risk factors, the precise mechanisms that underlie atrial fibrillation (AF) remain incompletely understood. AF is characterized by structural remodeling of the atria and, in particular atrial fibrosis. Inflammation has pivotal roles in fibrosis and recent evidence suggests that inflammation can contribute to the initiation and perpetuation of AF. We are working on a unique subset of T lymphocytes, named CD4+CD28null T cells, that expand in patients with acute coronary syndrome and chronic inflammatory disorders (e.g. rheumatoid arthritis). These cells have potent pro-inflammatory effects and secrete high levels of inflammatory cytokines interferon-gamma (IFN-g) and tumor necrosis factor-α (TNF-α), factors that promote fibrosis. Patients with lone AF have elevated levels of TNF-α, although its cellular source has not been investigated. Furthermore, production of IFN-g by T cells has been implicated in cardiac inflammation and fibrosis in animal models, whilst no information exists in AF patients. Our aim was to investigate inflammatory mechanisms underlying AF that focus on CD4+CD28null T cells, as the main source of IFN-g and TNF-α.
Methods: We recruited 60 patients with non-valvular AF who lacked co-morbidities associated with inflammation and coronary artery disease. The frequency of circulating CD4+CD28null T lymphocytes was quantified by flow cytometry in AF patients and age, gender and ethnicity matched healthy subjects. IFN-g and TNF-α serum levels were quantified by ELISA.
Results: We show for the first time that the percentage and number of CD4+CD28null T lymphocytes are significantly increased in AF patients compared to healthy subjects. No difference was detected in total CD4+ T lymphocytes and anti-inflammatory regulatory T cells, suggesting that AF patients have a specific expansion of pro-inflammatory CD4+CD28null T lymphocytes.
Conclusions: Our novel results show that AF patients have increased numbers of CD4+CD28null T cells that produce inflammatory cytokines IFN-g and TNF-α. This suggests that alterations in inflammatory T lymphocytes are present in AF, which may contribute to atrial structural remodeling. A better understanding of the role of lymphocytes and inflammation in AF may reveal new molecular targets in this disease.

P5285 | BENCH
Late INa increases diastolic SR Ca2+ leak in atrial myocardium through PKA and CaMKII

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An enhanced cardiac late Na current (late INa) as well as an increased sarcoplasmic reticulum (SR) Ca2+ leak are highly arrhythmogenic. This study aims to identify signalling pathways interconnecting late INa and SR Ca2+ leak in atrial cardiomyocytes (CMs).
Isolated atrial CMs from mice were paced at 3 Hz (20 beats) and than scanned for diastolic Ca2+ sparks (confocal microscopy, Fluo3-AM). The SR Ca2+ leak (spark frequency x amplitude x duration x width) was increased around 11-fold by the late INa enhancer ATX-II (0.5 nmol/L, n=43 vs 43, $P<0.05$). Ca2+/calmodulin-dependent protein kinase II (CaMKII) inhibition (AIP, 1μmol/L, n=48), inhibition of late INa (ranolazine, 10 μmol/L, n=32) as well as the Na+ channel blocker tetrodotoxin (2 μmol/L, n=28) all prevented ATX-II-dependent SR Ca2+ leak induction ($P<0.05$ each). The SR Ca2+ leak induction by ATX-II was further neither detected when the Na+/Ca2+-exchanger (NCX) was inhibited (KBR, 0.1 μmol/L, n=35 vs 34, $P<0.05$) nor in CaMKIIδc-KO mice (n=34 vs 27, $P<0.05$). Protein kinase A (PKA) inhibition (H89, 5 μmol/L) also decreased the ATX-II-induced SR Ca2+ leak (n=29 vs 66, $P<0.05$). FRET-measurements revealed increased cAMP-levels upon ATX-II (n=10 vs 10, $P<0.05$) suggesting that PKA is activated via cAMP upon late INa induction. Western blots showed a late INa-dependent hyperphosphorylation of CaMKII- as well as PKA targets at RyR2 (-S2815, -S2809) and PLB (-Thr17, -S16), which was prevented by H89 and AIP (n=4 and $P<0.05$ each). Late INa activation with ATX-II neither altered Ca2+ transient amplitudes (epifluorescence microscopy, 2 Hz, n=52 vs 65, P=0.97) nor SR Ca2+ load (n=37 vs 42, P=0.35). However, upon late INa activation and simultaneous CaMKII inhibition, Ca2+ transient amplitude (n=29 vs 65) and SR Ca2+ load (n=27 vs 42) were increased whereas PKA-inhibition reduced Ca2+ transient amplitude (n=16 vs 65) and load (n=15 vs 42) and slowed Ca2+ elimination kinetics ($P<0.05$ each). PKA thus facilitates CaMKII-dependent leak induction by activating SR Ca2+ accumulation. In atrial CMs from patients with atrial fibrillation (AF) an inhibition of late INa (ranolazine, n=15 vs 25) and CaMKII (AIP, n=34 vs 44) reduced the SR Ca2+ leak ($P<0.05$ each).
This study reveals that late INa activates CaMKII and PKA in atrial myocardium. Both kinases exert distinct effects on Ca2+ homeostasis and provoke SR Ca2+ leak. Thus, an inhibition of late INa represents a powerful approach to reduce CaMKII activity and decrease SR Ca2+ leak in atrial arrhythmias. The interconnection with the cAMP/PKA system further increases the antiarrhythmic potential of late INa inhibition.

VENTRICULAR TACHYCARDIA AND SUDDEN DEATH

P5287 | BEDSIDE
Low dose intravenous amiodarone is better for japanese patients with refractory ventricular fibrillation outside the hospital (a sos-kanto 2012 observational study interim report)

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Background: Intravenous amiodarone has been established as the first-line drug for cardiopulmonary resuscitation (CPR) in patients with fatal ventricular arrhythmias (VT/VF). According to the CPR guidelines of the American Heart Association, 300 mg bolus i.v. of amiodarone should be used for the initial dosage. On the other hand in Japan, 125 mg/10 min i.v. has been recommended for hemodynamic unstable VT/VF, while 150mg-300 mg bolus i.v. has been recommended for CPR. The purpose of this study is to investigate the appropriate initial dose of amiodarone for CPR.
Methods: We conducted a survey of survivors of out-of-hospital cardiac arrest (OHCA) in a region of Japan, a prospective, multicenter, observational study between January 2012 and March 2013. From the survey interim data, dose differential effect of amiodarone was investigated. Subjects were the adult patients with refractory VF who were performed more than two times of automatic external defibrillator (AED) or direct current shock (DC) during CPR by emergency medical service (EMS) or physicians. The endpoint was the successful rate of return of spontaneous circulation (ROSC), admission to the hospital, and 24hrs survival rate.
Results: Of the 5,875 adult patients with OHCA, 421 (7.2%) were VF, 1153 (19.6%) were pulseless electrical activity (PEA), 3,756 (63.9%) were asystole, and 399 (6.8%) were others. By the effect of basic and advanced cardiac life supports by EMS and physicians, DC-resistant VT/VF were recognized in the 577 patients. Of these patients, 237 were treated with anti-arrhythmic drugs; nifekalant, lidocaine, or amiodarone. Intravenous amiodarone was used for the 134 patients; for initial dose, 22 (16.4%) were administered 125 mg/10 min i.v., 35 (26.1%) were 150mg bolus i.v., 64 (47.8%) were 300mg bolus i.v., and 13 (9.7%) were others. The ROSC rate was 16 (72.7%) in the 125mg group, 13 (37.1%) in the 150mg group, and 21 (32.8%) in the 300mg group ($p<0.01$). The admission rate was 13 (59.6%), 17 (48.6%), and 20 (31.3%) respectively ($p<0.01$). The 24hrs survival rates were similar between 125mg group (50.0%) and 150mg group (48.6%), and significantly superior than 300mg group (20.3%). In the background there was no significant difference between 3 groups in the item of male, bystander witness, age, height, bodyweight, DC times, adrenaline dose, serum potassium, and serum creatinine.
Conclusion: Low dose intravenous amiodarone resulted in better ROSC, admission and 24hrs survival rates than that of 300mg amiodarone in patients with refractory VF.

P5288 | BEDSIDE
Clinical features and prognosis of patients who survived cardiac arrest due to coronary spasm

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Purpose: Coronary artery spasm can lead to lethal arrhythmia and sudden cardiac death. The purpose of this study was to elucidate the clinical features and prognosis of patients who survived cardiac arrest due to coronary spasm.
Methods: We retrospectively studied consecutive patients who survived cardiac arrest due to coronary spasm and admitted to our university medical center between September 2007 and September 2013.
Results: Nineteen patients (18 men and 1 woman, mean age 55±11 years) were enrolled in the present study. Ventricular fibrillation (VF) was documented as the initial rhythm at cardiac arrest in 18 patients, and pulseless electrical activity was in 1 patients. Transient ST-segment elevation during spontaneous attack was observed in 9 patients. Acetylcholine provocation test was performed and resulted in positive in 15 patients. In 10 patients of the study population, cardiac arrest was the first episode of coronary spasm attack. All patients were treated with at least 2 vasodilators including calcium channel blockers. An implantable defibrillator (ICD) was implanted in 10 patients according to the discretion of the attending physician. During a mean follow-up interval of 21 months, 4 episodes of VF were observed in 3 patients and ST-segment elevation myocardial infarction (STEMI) was observed in 1 patient. Two episodes of VF were occurred before the diagnosis of coronary spasm was confirmed during the index hospitalization, and were

treated by manual defibrillation. The other 2 VF were occurred in patients who were implanted ICD, and treated by appropriate ICD shocks. No patients died during the follow-up period. There are no differences in the characteristics of the patients between those with and without recurrence of lethal arrhythmia and acute myocardial infarction. However, medications for coronary spasm were discontinued before the events in all patients who developed VF and STEMI. The intervals between discontinuation of medications and cardiac events were less than 2 days in all events.
Conclusions: The patients who survived cardiac arrest due to coronary spasm were at high risk for recurrence of severe ischemia and lethal arrhythmia. Discontinuation of medication, even within a few days, was closely associated with the cardiac events. ICD therapy may be beneficial in patients who survived cardiac arrest.

P5289 | BEDSIDE
Long-term follow-up of asymptomatic Brugada syndrome

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Purpose of the study: To report the follow-up of asymptomatic Brugada syndrome (BS) and to study the events according to familial history and results of programmed ventricular stimulation (PVS). The prognosis of asymptomatic BS remains questionable.
Methods: 43 asymptomatic patients, 38 males, 5 females with a type 1 Brugada pattern were studied; 20 patients had a family history of sudden death (SD); age varied from 23 to 74 years (mean 46±13). All patients underwent echocardiography, exercise testing and Holter monitoring. PVS was performed in all except in 7 patients who refused the study. ICD was implanted in 24 patients (3 patients refused the ICD implantation). Two asymptomatic patients without familial history of SD, but with inducible VF were treated by hydroquinidine and PVS became negative. Implantable loop recorder was used in 12 patients. Mean follow-up was 6±3.9 years.
Results: At PVS, VF was induced in 16 patients (44%), non-sustained (NS) VF (29.4±11 sec) in 6 patients (17%). PVS remained negative in remaining 14 patients (39%). During follow-up, 2 patients in whom PVS was not performed died suddenly; 2 patients with ICD had a ventricular fibrillation (VF). Another patient died from unknown death. Prevalence of death was 11.6%. One patient had a NS VF. VF induction did not predict the occurrence of death or VF (sensitivity 50%, specificity 56%). VF and non-sustained VF induction did not add a benefit for the prediction of arrhythmic event. The risk factors for a serious event were the male gender (no death in women) and the history of familial sudden death (all SD's or VF in patients with familial SD but in 1 of them, SD was debatable (occurring at 70 years).
Conclusions: Prevalence of deaths was high in these young patients without heart disease. PVS has a low sensitivity and specificity (about 50%) for the prediction of a significant clinical event. Only female gender was a factor of good prognosis. Familial history of SD was a significant predictor of major event in our population.

P5290 | SPOTLIGHT
Two novel SCN1B variants (V169M in SCN1B1 and G266S in SCN1B2) increased late sodium current in a Sudden Arrhythmic Death Syndrome patient

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Purpose: A 17-year-old boy suffered from sudden arrhythmic death syndrome. The aim of this study was to elucidate the electrophysiology mechanism of these arrhythmic events.
Methods and results: We obtained DNA from patient and sequenced the coding region of KCNQ1, KCNH2, SCN5A, SCN1B, RYR2, and GPD1L genes. Two mutations in SCN1B1 (V169M) and SCN1B2 (G266S) were identified. Chinese hamster ovary (CHO) cells were used to co-express hNav1.5 with either wild-type or mutant Navβ1 subunits (V169M, G266S or ½V169M+½G266S) to recapitulate the cardiac sodium current (INa). Whole-cell patch clamp recording showed that V169M channels had depolarizing shifts in steady-state activation, while V169M/G266S combination turned this activation curve to a small but significant hyperpolarizing direction, as compared to their respective wild type. Besides, G266S and V169M/G266S resulted in significant hyperpolarizing shifts in steady-state inactivation as well as prolonged their time to half recovery from inactivation at -85mV, as compared with wild type. Moreover, we found that these two mutations (V169M or G266S or V169M/G266S) caused a 2-3 fold (compared with WT-β1 or WT-β1b or WT-β1+WT-β1b) increase in late sodium current, which contributed to the electrophysiological property subjected to SADS-relevant lethal arrhythmias.
Conclusions: We identified two new pathogenic variants in SCN1B that appeared to be present on a SADS patient. Functional investigations of the mutations revealed increased sustained sodium current, and therefore might be multiple disease-causing.

P5291 | BEDSIDE
Role of cardiac arrhythmias in sudden cardiac death in renal transplant candidates

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Purpose: The single largest cause of death in renal transplant candidates (RTC) is sudden cardiac death (SCD), accounting for roughly 25%. This study investigated the role of arrhythmic events (AE) diagnosed by implantable loop recorder (ILR) in sudden cardiac death in RTC.
Methods: Prospective observational study performed between June/2009 and January/2011. One hundred consecutive RTC underwent ILR implantantion to monitor cardiac rhythm for at least one year. AE were classified in bradyarrhythmias, atrial tachycardia (AT), atrial fibrillation (AF), non-sustained (NSVT) and sustained ventricular tachycardia (SVT). Groups were compared by Mann–Whitney U test, Chi square test or Fisher's exact test, as appropriate. Multivariate logistic regression models were developed to determine risk predictors of AE and death.
Results: The average age was 59±8.8 years, with predominance of men (65%). Hemodialysis mean time was 53±30 months. Echocardiography characteristics showed left ventricular ejection fraction (LVEF) of 59±10%. During mean follow-up of 2.9±1.3 years 33% patients died. We were unable to identify the cause of death in 4 (12.1%). The causes of death were sepsis (33.3%), SCD (21.2%), renal complications (12.1%), pulmonary (6.0%) and one of each cause: heart failure, myocardial infarction, stroke, hypovolemic shock and renal transplant complication. During mean ILR monitoring of 424±127 days, AE was detected in 73% of patients. Bradyarrhythmias were present in 25%, AT/AF in 18%, NSVT in 56% and one patient presented SVT. AE was detected in 71.4% of patients with SCD, 68.1% in non-SCD patients and 73% in survivors, therefore the presence of AE was not associated with SCD (P=0.830). Left ventricular dilatation was independently associated with TVNS (OR 2.83 [95%CI 1.01-7.96] P=0.041). The use of hypoglycemic drugs (OR 2.5 [95%CI 1.01-6.19] P=0.047) and PR interval (OR 1.03 [95%CI 1.01-1.06] P=0.017) were independent predictors of death.
Conclusions: Renal transplant candidates had a high incidence of AE and SCD accounted for almost a quarter of the identifiable causes of death, however the AE were not associated with SCD.

P5292 | BENCH
Next-generation sequencing data strengthens the involvement of cardiac structural diseases in Sudden Infant Death Syndrome (SIDS)

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The Sudden Infant Death Syndrome (SIDS) represents the most prevalent cause of death in children less than 1 year of age in developed countries. Cardiac channelopathies have been found to be responsible of a significant percentage of SIDS cases, but the involvement of other sudden cardiac death-related (SCD) diseases such as Hypertrophic (HCM), Dilated (DCM) or Arrhythmogenic Right Ventricular (ARVC) cardiomyopathies as the underlying cause of some cases in the absence of a visible phenotype remains currently poorly known. We had previously reported the presence of known HCM-associated mutations in a big cohort of 286 unrelated SIDS cases using high-throughput genotyping techniques. Some of them have shown to produce defective proteins that disrupt the sarcomeric Ca2+ homeostasis which may ultimately affect the cardiac contractile properties leading to disease phenotypes. Here, we present our results from the study of a SIDS cohort composed of 41 unrelated cases underwent massively parallel sequencing of 81 genes, mainly arrhythmogenic, structural, and aortic disease-related genes associated with increased risk of SCD. Computational filtering of the output data was based on correlation with altered function of the proteins (missense, nonsense, frameshift, splicing or ncRNA variants), allele frequency within populations and measures of quality and sequence read mapping. As a result, 62 validated variants were categorized as a function of their pathogenic likelihood, according to current recommendations. A total of 36 variants (58%) were novel and, therefore, classified as "variants of uncertain significance". This category also gathers 20 variants (32%) reported in population studies without any clinical association and 4 variants (6.5%) initially reported as disease-causing but lacking conclusive supporting evidence of causation. Interestingly, we also found 2 missense variants (3.5%) in MYL2 and TTN genes previously associated with HCM and myopathy, respectively. After a review of the literature, public and private databases, we categorized these variants as "likely pathogenic", since several primary reports as disease-associated are available for each variant and functional studies support a partial involvement of the dysfunctional proteins in the disease development, although more further studies are necessary to consider them as "pathogenic". These and previous results are altogether encouraging and the fast development of Next-Generation Sequecing platforms have widened the limits of research in

a more affordable way, providing huge amounts of information that were formerly barely accessible.

P5293 | BEDSIDE
Usefulness of approximate body-surface-potential-mapping (a-bspm) for risk stratification

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Purpose: Despite progress in the treatment of cardiovascular disease, the incidence of sudden cardiac death (SCD) remains high. There is a multitude risk stratification techniques, but even those recommended by the current guidelines lack precision, and prediction of appropriate implantable-cardioverter defibrillator (ICD) shocks is particularly difficult. The Approximate Body Surface Potential Mapping (A-BSPM) is a method using the standard 12-lead surface electrocardiogram for constructing a map of the cardiac electric potentials projected onto the body surface. We evaluated A-BSPM as a predictor of risk represented by appropriate ICD discharge and mortality in ICD patients (pts).
Methods: A total of consecutive 103 ICD pts [mean age 63±14 years, 53% ICM, 22% DCM, 25% other CM, 63% primary prophylaxis (PrimP), were included and A-BSPM was recorded before first ICD implantation. Pts with atrial fibrillation or frequent premature ventricular ectopic beats were excluded. Follow up (FU) data were obtained from the ICD clinic file or by telephone or written contact with patients or general practitioners. Co-primary endpoints were all-cause mortality and appropriate shock. The predictive value of multiple available and dichotomized A-BSPM parameters was determined by using Kaplan-Meier survival curves (KM), chi-square tests (CHI), and calculation of ROC areas. A selection of the best parameters is presented.
Results: The mean FU of the included pts was 31±11 months. In this period, 11 appropriate ICD shocks occurred and 15 patients died. Two of the eight selected A-BSPM parameters were significantly associated with shock incidence [npTa1 (number of positives T-waves >1 mV): KM logRank p=0,032, HR 4,6 (95%KI 1,4 - 14,9), CHI p=0,028; npTa2 (number of positives T-waves >2 mV): KM logRank p=0,046, HR 4,2 (95%KI 1,3 – 13,7), CHI p=0,039]. One additional parameter was significantly associated with mortality [spQRSint (sum of positive QRS integrals): KM logRank p=0,025, HR 3,3 (95%KI 1,2 – 9,2), CHI p=0,046].
Conclusion: Electrocardiographic mapping of body surface potentials using the A-BSPM method reveals promising identification of patients with a higher risk of appropriate ICD shocks. The parameters can be derived using any digital 12-lead ECG, calculation is fully automatic and reproducible.

P5294 | BEDSIDE
Inferior J-wave is associated with ventricular fibrillation related poor prognosis in patients with anterior ST-elevation myocardial infarction: long-term outcome

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Introduction: In patients without structural heart disease, the presence of J-wave on electrocardiography (ECG) is associated with ventricular fibrillation (VF) and sudden cardiac death (SCD). Especially, the presence of inferior J-wave is a strong risk marker of long-term mortality. However, the significance of J-wave in patients with acute myocardial infarction (AMI) is not clear.
Methods: We studied consecutive 197 patients with first anterior acute ST-elevation MI. ECGs of 86 patients could be evaluated before the AMI onset. ECGs of remained patients were evaluated after ST resolution. J-wave was defined as an elevation of the QRS-ST junction (≧0.1mV) in inferior lead, manifested as QRS slurring or notching. VF in this study was defined as that occurring within 24 hours from the AMI onset, not terminating spontaneously, and requiring electrical cardioversion. Patients were classified into 2 groups;J-wave group (n=36) or non J-wave group (n=161), and were followed for 37 months.
Results: Clinical characteristics including sex, Killip class, the time from onset to admission were similar between the 2 groups. However, the J-wave group patients showed significantly higher incidence of VF than the non J-wave group patients{n=10 (27%) vs. n=11 (7%), p<0.001}. In addition, incidence of repetitive VF was significantly higher in the J-wave group than in the non J-wave group{n=5 (14%) vs. n=2 (1%), p<0.001}. Multivariate analysis revealed that independent predictors of VF occurrences were J-wave (odds ratio=9.51; 95%CI 2.84-36.07; p<0.001) and Killip class≧2 (odds ratio=9.3; 95%CI; 2.35-40.27; p<0.01). Additionally, despite similar infarct size and left ventricular function, incidence of VF related death during hospitalization or SCD during follow-up was significantly higher in the J-wave group than in the non J-wave group {n=3 (8%) vs. n=3 (2%), p=0.02}. Independent predictors of VF related Death or SCD were chronic kidney disease (odds ratio=11.28; 95%CI 1.07-194.4; p=0.04) and J-wave (odds ratio=8.58; 95%CI 1.0-107.96; p<0.05).
Conclusions: In anterior ST-elevation myocardial infarction, the presence of inferior J-wave appears to be a risk marker of not only VF occurrences, but also poor prognosis.

P5295 | BEDSIDE
N-terminal prohormone of brain natriuretic peptide (NT-proBNP) as early independent predictor of outcome in patients after cardiac arrest and return of spontaneous circulation in patients with the acu

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Background: The purpose of this study was to assess and compare the capability of NT-proBNP, cardiac troponin T (cTnT), serum neuron-specific enolase (NSE) and protein S100B, as biomarkers of myocardial necrosis and hypoxic brain damage, to predict neurological outcome in patients after out-of-hospital resuscitation (CPR).
Methods: 60 patients (45 males, 60.9±13 years), were evaluated after CPR for the ventricular fibrillation (VF) during an acute myocardial infarction (AMI). All patients were indicated for urgent coronary angiography, echocardiography for left ventricular ejection fraction (LVEF) estimation using Simpson biplane formula and treated with mild therapeutic hypothermia (MTH) using intravascular temperature management to maintain target temperature (33°C) for 24 hours (Thermogard XP, ICY catheter, Zoll). The Cerebral Performance Categories scale (CPC) was used as the outcome measure; a CPC of 3-5 was regarded as a poor outcome, and a CPC of 1-2 a good outcome. Measurements of serum NT-proBNP, cTnT, NSE and S100 were performed within 2 h after admission, as well as on 2nd, 3rd, 4th day after the time of cardiac arrest (CA).
Results: Neurological status was evaluated according to the CPC scores at 3 months after CA and patients were divided into 2 subgroups: CPC1+2 - good outcome (n=29, 48%) and CPC 3-5 - serious neurological impairment, coma or death as a poor outcome (n=31, 52%). Baseline NT-proBNP (ng/mL) was significantly higher in patients with poor outcomes: 3462±3224 vs. 1011±1193, p<0.0001. Baseline and 2nd day NSE (ng/mL) were not different, but significant differences on 3rd, 4th day after CA were found: NSE on 3rd day: 71.4±70.6 vs. 22.4±11.7 (p<0.002); and NSE 4th day: 83.3±112 vs. 14.8±9.1 (p<0.0011). No significant differences were found in return of spontaneous circulation (ROCS) interval (22±12 vs. 26±13 min., p=NS), baseline S100, cTnT (baseline 0.51±1,95 vs. 0.58±1,21, 2nd day 1.69±1.94 vs. 1.84±2.72 μg/L, p=NS), baseline LVEF (40.7±7.3 vs. 7.6±9.6%, P=NS) in comparison of subgroups with good and poor outcome. ROC curve for good outcome showed AUC of 0.83 (95%CI 0.72-0.94, p<0.0001) and identified optimal cut-off of NT-proBNP<1095 ng/mL to predict good outcome with a specificity of 81% [95%CI 63-93], sensitivity of 83% [95%CI 64-94], a positive predictive value of 80% and a negative predictive value of 83%.
Conclusion: In patient after CPR for VF during AMI, baseline NT-proBNP gives reliable and on LVEF resp. AMI extent independent information concerning outcome after CPR and could be used as an early marker of hypoxic brain damage.
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P5296 | BEDSIDE
Preexcitation syndrome in the elderly patients. Why should they be managed as young patients?

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Purpose of study: To look for the influence of advanced age on clinical data and long-term follow-up of patients with a preexcitation syndrome (PS). Age-related differences were reported for PS.
Methods: 886 patients, 545 males, 341 females, aged from 5 to 85 years, mean 33.5±17, were referred for PS and electrophysiological study (EPS). Clinical history, echocardiography and treatment were collected. Patients were followed from 3 months up to 10 years (5.4±5 years).
Results: 68 patients were aged from 60 to 85 years (group I) (mean age 68±6); 818 patients were aged less than 60 years (group II) (mean age 31±14). Underlying heart disease (HD) was more frequent in group I (20.5%) than in group II (6.5%) (p<0.0001), but congenital HD (n=25) was only present in patients <36 years. Gender did not differ. Accessory pathway (AP) location did not differ for posteroseptal (52.5 vs 45.5%) and left lateral location (45.5 vs 36%) in groups I and II. Right lateral, anteroseptal and nodoventricular AP's were only noted in group II (5.5, 11, 2%), except in one case: one nodoventricular AP was identified in a man of 81 years in which ablation was done successfully for wide QRS tachycardia. Group I was more frequently symptomatic than group II (79 vs 63%) (p<0.007): presentation as syncope or reentrant tachycardia did not differ (16%, 41% in group I vs 12%, 41% in group II), but presentation with atrial fibrillation (AF) or a poorly-tolerated tachycardia requiring electrical shock was more frequent in group I (7%, 15%) than in group II (3%, 7%) (p<0.04, <0.01). During follow-up, AP ablation was indicated as frequently in group I (43%) and II (45%). Failure or recurrence requiring a 2nd procedure was similar in group I (21%) and II (15%). In untreated patients, late occurrence of AF was as frequent in group I and II (13%, 6%), but late poorly-tolerated tachycardia was more frequent in group I (8%) than in group II (0.7%) (p<0.0002).
Conclusions: The prevalence of preexcitation syndrome was low in patients >59 years (7.7% and rare after 69 years (2.6%). Right lateral, anteroseptal AP and

nodoventricular AP's were exceptional after 59 years. Elderly patients were more frequently symptomatic with a higher risk of AF and of poorly-tolerated tachycardia than younger patients. Therefore elderly patients with a preexcitation syndrome require the same management as younger patients.

NON-INVASIVE STUDIES

P5298 | BENCH
Impaired heart rate recovery index in patients with sarcoidosis

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Introduction: Sarcoidosis, an inflammatory granulomatous disease, associated with various cardiac disorders, including threatening ventricular arrhythmias and sudden cardiac death. Heart rate recovery after exercise is a function of vagal reactivation, and its impairment is an independent prognostic indicator for cardiovascular and all-cause mortality. The aim of our study was to evaluate heart rate recovery in patients with sarcoidosis.
Methods: The study population included 56 patients with sarcoidosis (23 men, mean age = 47.3±13.0 years, and mean disease duration = 38.4±9.7 months) and 54 healthy control subjects (20 men, and mean age = 46.5±12.9 years). Basal electrocardiography, echocardiography, and treadmill exercise testing were performed in all patients and control participants. The heart rate recovery index was defined as the reduction in the heart rate at peak exercise to the rate 1st-minute (HRR1), 2nd-minute (HRR2), 3rd-minute (HRR3) and 5th-minute (HRR5) after the cessation of exercise stress testing.
Results: There are significant differences in HRR1 and HRR2 indices between patients with sarcoidosis and control group (24.9±6.4 vs 33.7±10.8; $p<0.001$ and 45.4±9.9 vs 53.2±11.9; $p<0.001$, respectively). Similarly, HRR3 and HRR5 indices of the recovery period were lower in patients with sarcoidosis, when compared with indices in the control group (52.7±12.4 vs 60.8. ± 13.0; $p<0.001$ and 59.8±12.9 vs 68.2±12.6; $p<0.001$, respectively) (Figure). Exercise capacity was notably lower (9.2±2.1 vs 11.6±2.8 METs; p=0.001, respectively) and systolic pulmonary arterial pressure at rest was significantly higher in patients with sarcoidosis compared with control group (29.7±5.5 mm Hg vs. 25.6±5.7 mm Hg, p=0.001, respectively). Furthermore, we demonstrated that HRR indices were related with radiographic stage.
Conclusions: The heart rate recovery index impaired in patients with sarcoidosis as compared with control subjects. When the prognostic significance of the heart rate recovery index is considered, these results may partially explain the increased occurrence of arrhythmias and sudden cardiac death in patients with sarcoidosis. This study calls attention to the importance of heart rate recovery index that may be clinically helpful in the recognition of high-risk patients.

P5299 | BEDSIDE
Electrocardiographic markers of arrhythmogenic risk in left ventricular hypertrophy

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Purpose: Left ventricular hypertrophy (LVH) is considered a risk factor for malignant arrhythmias and sudden cardiac death (SCD). The aim of the study was to assess non-invasive markers of SCD in patients with LVH of various aetiology. Additionally, the relationship between electrocardiographic markers and aetiology, type and degree of LVH were assessed.
Methods: Study group consisted of 77 subjects with echocardiographic features of LVH, and was divided into 3 groups: 27 patients with primary hypertrophic cardiomyopathy HCM (group 1), 27 age-matched patients with hypertension (HTN) related LVH (group 2) and 23 subjects with athlete's heart (group 3). LVH was confirmed in transthoracic echocardiography. Minimal IVS thickness for group 2 and 3 was 12mm. In all subjects late potentials (LP), heart rate variability (HRV), heart rate turbulence (HRT), and microvolt T-wave alternans (MTWA) using Holter method were assessed.
Results: Markers of disturbed repolarization (positive late potentials and TWA>100μV) were most frequent in HCM group, and least frequent in athletes. HRV as well as HRT parameters were the most unfavourable in HTN-LVH group, while in athlete's heart group, despite similar grade of LV hypertrophy, were normal. There were no significant correlation between studied HRV, HRT, LP and TWA parameters and degree LV muscle thickness or type of hypertrophy.
Conclusion: Different aetiology of LVH is associated with various distribution of electrocardiographic markers of SCD. Markers of disturbed repolarization are more frequently observed in HCM group, while HRV and HRT parameters are most unfavourable in HTN-LVH. In athletes with LVH markers of SCD are uncommon which suggests good prognosis in this type of LV hypertrophy.

P5300 | BEDSIDE
The activation of RASS and sympathetic nervous system in patients with vasovagal syncope

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The renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system are important in the maintenance of vertical position. They both are activated with time and the duration of tilt testing may influence the activation. The aim of the study was to assess the activation of RAAS and catecholamines during tilt-induced vasovagal syncope.
The study population consisted of 192 patients (F 140, M 52), aged 49.8±19.3 years, with the vasovagal syncope during diagnostic tilt testing. Plasma renin activity (PRA) and aldosterone were measured in a supine position before test (1), immediately after syncope (2) and 10 minutes after syncope (3). Adrenaline and noradrenalin were measured at (1) and (2). The groups were divided according to the phase of tilt test in which syncope occurred.
Results are shown in the table.

	Passive phase N=63	NTG provocation N=129	p
Female sex (%)	66.7	76.0	n.s.
Age (years)	45.8±21.3	51.7±18.0	<0.05
Instrumentation injection blood phobia (%)	17.5	7.8	<0.05
VASIS II	50.8	43.4	n.s.
PRA 1 (ng/ml/h)	2.0±2.2	1.6±1.8	n.s.
PRA 2 (ng/ml/h)	4.7±4.2*	6.1±5.7*	<0.05
PRA 3 (ng/ml/h)	4.4±4.3*	5.1±4.6*&	n.s.
Aldosterone 1 (pg/ml)	85.0±72.9	74.7±51.1	n.s.
Aldosterone 2 (pg/ml)	168.0±175.0*	166.8±121.2*	n.s.
Aldosterone 3 (pg/ml)	175.8±91.9*&	209.9±116.5*	<0.05
Noradrenaline 1 (nmol/l)	3.2±1.9	2.2±1.1	<0.05
Noradrenaline 2 (nmol/l)	5.8±10.5*	3.2±1.5*	<0.05
Adrenaline 1 (nmol/l)	1.1±1.0	1.1±0.5	n.s.
Adrenaline 2 (nmol/l)	1.7±1.2*	1.8±0.8*	n.s.

*p<0.05 vs baseline values, &p<0.05 vs previous value.

There were several differences between the groups listed in the table. The activation of RAAS is diminished in patients with syncope during the passive phase of the test despite of pronounced activation of sympathetic nervous system.
Conclusions: In patients with syncope in the passive phase of tilt test the activation of RAAS is disturbed. The enhanced sympathetic activity in this settings could be responsible for neurocardiogenic reaction induction.

P5301 | BEDSIDE
Analysis of heart rate variability and T wave alternans during head-up tilt test

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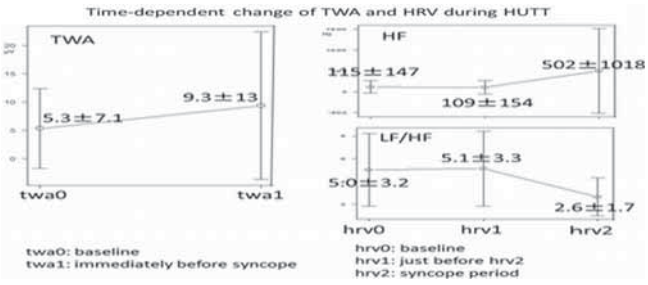
Purpose: Vasovagal syncope (VVS) has relation to abnormalities of autonomic nerve system (ANS). Using ambulatory electrocardiographic monitoring (Holter ECG) during head-up tilt test (HUTT), we can analyze heart rate variability (HRV) and T wave alternans (TWA). Many studies report about relation between VVS and HRV, however there has been no clinical study exploring the changes of TWA during HUTT. The aim of this study is to investigate the changes of TWA during HUTT.
Methods: We performed HUTT in 93 consecutive patients with syncope (aged 57±21 years, 65 males and 28 females). Using Holter ECG during HUTT, we analyzed modified moving average (MMA) TWA by time domain analysis at baseline (twa0) and immediately before syncope (twa1). Furthermore, we analyzed



Time-dependent change of TWA and HRV.

Abstract P5299 – Table 1. Markers of electrical instability

	Age	IVS (mm)	LVMI (g/m²)	SDNN (ms)	LF/HF	LP n (n%)	HRT n (n%)	TWA n (n%)
1. HCM (n=27)	54±13.4	2.0±0.48	215±90.2	133±57.4	1.8±1.18	8 (30%)	6 (22%)	12 (44%)
2. HTN-LVH (n=27)	59±6.1	1.45±0.17*	163±31.6*	112±27.1	4.0±5.26*	7 (26%)	11* (41%)	6* (22%)
Athlete's heart (n=23)	34±12.0	1.23±0.06*#	150±27.0*	200±51.5*#	3.2±1.27	5* (22%)	4# (17%)	4* (17%)

Data presented as average ±SD. *p<0.05 vs HCM, #p<0.05 vs HTN-LVH.

HRV by spectral analysis for each five minutes at baseline (hrv0), syncope period (hrv2), and just before hrv2 (hrv1).
Results: Forty-four patients were diagnosed as VVS by HUTT (mixed type: 20, cardioinhibitory type: 7, vasodepressor type: 17). In patients with VVS, TWA values in twa0 and twa1 were 5.3±7.1, 9.3±13μV respectively, and the TWA value was significantly higher just before syncope than that at baseline (p=0.038). Average HF values of HRV in hrv0, hrv1, hrv2 were 115±147, 109±154, 502±1018Hz ($p=6.3\times10^{-8}$) respectively, and average LF/HF values were 5.0±3.2, 5.1±3.3, 2.6±1.7 ($p=3.6\times10^{-6}$) respectively.
Conclusions: TWA value was significantly higher in just before syncope than that at baseline. By analyzing HRV during HUTT, parasympathetic tone was abruptly augmented in conjunction with suppression of sympathetic tone just before syncope. Therefore the fluctuation of TWA values may associate with ANS. Conclusively this study suggested that such abrupt change of ANS might influence on myocardial repolarization.

P5302 | BEDSIDE
Usefulness of electrical velocimetry (EV) during head up tilt testing (HUTT) for vasovagal syncope

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Electrical velocimetry delivers beat-to-beat monitoring of cardiac output (CO), stroke volume (SV) and systemic vascular resistance (SVR) using an original algorithm based on thoracic bioimpedance changes using standard ECG electrodes without continuous BP recording.
The aim of the paper was to evaluate the efficacy of the non-invasive beat-to-beat monitoring of CO, SV and SVR performed by the method of EV as alternative to continuous blood pressure (BP) monitoring by more sophisticated and expensive devices.
Methods: HUTT with nitroglycerine challenge was performed using the Italian protocol in 32 patients with syncope of unknown etiology after initial evaluation. Hemodynamic parameters were recorded beat-to-beat by Aesculon-Osypka monitor using 4 standard ECG electrodes. Non-invasive BP was measured manually using the same monitoring device.
Results: HUTT was positive in 28 patients. NTG was used in 19 patients. The SVR (dyns/cm5/m^2) decreased in vasodepressor and mixed HUTT (+) patients from 1950±423 at baseline to 1273±227 (p=0,01) at symptom onset and further to 870±155 (p<0,01). The respective values of CO (l/min) and SV (ml) were: 4,4±1 vs. 4,1±0,7 (p=0,1) and 53±11,2 vs. 51,2±9 (p=0,1).These were associated with corresponding changes in BP and HR. Positive HUTT was predicted by a decrease of more than 25% of the SVR in the minute before symptom onset in 22 patients.
Conclusion: In our study electrical velocimetry was able to demonstrate the hemodynamic substrate of the HUTT induced syncope and was able to predict the outcome of the test in the most cases. Comparative study with other techniques are technical feasible and could provide further data on its usefulness

P5303 | BEDSIDE
Is it true that the more a syncopal episode seems to be vasovagal by its description, the greater the prevalence of a positive tilt test?

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Two methods are used to diagnose vaso-vagal syncope (VVS): the anamnesis and the head-up tilt test (TT). None of them meets the conditions to be considered as a gold standard. Some clinical criteria were proposed as predictors of a positive (+) TT. However the results are divergent. With the aim of evaluating whether the sum of criteria suggesting a VVS by anamnesis was related to a higher prevalence of (+) TT, 321 patients (pts) with syncope (44.9±21.6 years, 193 women) were evaluated. All of them filled out a questionnaire describing the last episode and a TT was performed.The variables describing the episode were grouped as follows: For a) Vaso-vagal suspicion: 1-circumstances, 2-prodroms and 3-symptoms during the recovery phase and, b) Cardiac suspicion: 1-circumstances, 2-prodroms, 3-peri-episode findings.One point was assigned for each present item. Each episode could have between 0 and 3 criteria for VVS and between 0 and 3 criteria for cardiac suspicion.The prevalence of (+) TT for each score was analyzed.

Table 1
Prevalence of (+) TT for each score

		(+) TT	% (+) TT	p
Vaso-vagal criteria	0	21/73	28.8	
	1	36/113	31.9	
	2	30/105	28.6	0.44
	3	5/30	16.7	
Cardiogenic criteria	0	29/92	31.5	
	1	39/134	29.1	0.26
	2	17/78	21.8	
	3	7/17	41.1	

Results: Ses Table 1. In addition, prevalence of (+) TT was similar in pts. with different underlying diseases and in both genders. No correlation was found between age and (+) TT.
Conclusions: 1. A high suspicion of vaso-vagal etiology of syncope by adding different criteria of the anamnesis is not related to a higher prevalence of (+) TT. 2. The information provided by the anamnesis and the tilt test is not redundant.

P5304 | BEDSIDE
Estimation of possible syncope-induced brain injury and clotting disturbances during positive head-up tilt test in patients with vasovagal syndrome

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Syncope is an effect of temporal, global hypoperfusion of brain. It is known that even short episodes of circulatory arrest may lead to brain injury. Some release of brain injury markers - neuron-specific enolase (NSE) as well as clotting disturbances was described in relation to tilt-test (HUTT) induced syncope in patients with vasovagal syncope.
Aim of study: Evaluation of injuring influence of vasovagal syncope (VVS) on the brain evaluated by release of NSE, in relation to clotting changes during HUTT in pts. with VVS.
Study population: 60 pts. (38 women) aged 18-74yrs (mean age 35,6), with VVS, referred to HUTT.
Methods: All pts. underwent standard HUTT. All pts. lies at supine position by 30 minutes after antecubiltal vein canniulation. Blood sample for NSE evaluation was collected before and 1 hour after HUTT. Before HUTT and at the onset of HUTT-provoked syncope blood sample was collected for analysis of clotting parameters: prothrombin time (INR), activated partial thromboplastin time APTT, serum concentrations of fibrinogen (FIB) and d-dimer (d-Dim).
Results: HUTT was positive in 51 pts. (85,0%). Significant increase of NSE level after HUTT in all pts. With HUTT-induced syncope, (3,3 vs. 4,2 ng/ml; p<0,01) was observed. There were no significant increase of NSE in pts. with negative HUTT. Substantial increase of serum levels of FIB (3,1 to 3,3 g/l p<0,006), d-Dim (263,0 vs 379,0 ug/l; p<0,001), with decrease of APTT (30,9 to 25,6 s; p<0,0001) and INR (1,1 vs 1,03; p<0,03) were observed in patient fainted during HUTT. Correlation between syncope induced rise of NSE and d-dimer level before HUTT (K=0,32; p<0,04) and after the test (K=-0,35; p<0,04) were found. It suggest that activation of fibrinolysis revealing by rise of d-dimer concentration may protect the brain injury related to the syncope induced by orthostatic stress.
Conclusions: Syncope induced by orthostatic stress during tilt test in pts. With vasovagal syncope is concerned both release of brain injury markers and induction of changes in clotting-fibrillation process.
Endogenous activation of fibrinolysis during HUTT-induced syncope, revealing by rise of d-dimer concentration, may protect against of brain injury related to clinical circumstances in patients with vasovagal syncope.

P5305 | BEDSIDE
Influence of sleep disordered breathing on heart rate turbulence in heart failure patients

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Purpose: Sleep-disordered breathing (SDB) is associated with adverse outcomes in patients with heart failure (HF). Heart rate turbulence assessed by Holter ECG has been used in order to predict sudden cardiac death. Recent studies have suggested that heart rate turbulence has a predictive value for adverse prognosis in HF patients. We investigated the relationship between SDB and heart rate turbulence in HF patients.
Methods: In this study, 75 patients with HF and SDB were examined. Patients with atrial fibrillation and receiving implantable pacemaker device therapy were excluded. We simultaneously performed Holter ECG during 24-hr period and polysomnography in night time, and examined apnea hypopnea index (AHI) and heart rate turbulence (turbulence onset and turbulence slope) during 24-hr period.
Results: All patients were divided into two groups based on the presence of severe SDB: Group A (AHI<30, n=58) and Group B (AHI≥30, n=17). Turbulence slope was significantly lower in Group B than in Group A during 24-hr period (night time: 6.9 vs. 3.6; day time: 7.0 vs. 3.7; all day: 6.6 vs. 3.5 ms/RR, P<0.05, respectively). Turbulence onset did not differ between two groups (night time: 0

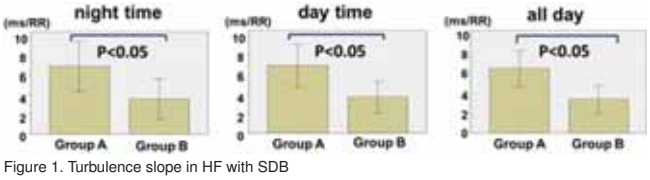

Figure 1. Turbulence slope in HF with SDB

vs. 0; day time: -0.01 vs. 0; all day: 0 vs. 0%, respectively). Importantly, blunted turbulence slope was observed across a 24-hour in patients with severe SDB (Fig. 1).
Conclusions: Common pathological mechanisms underlying SDB and HF, leading to baroreceptor reflex suppression, were associated with abnormal heart rhythm turbulence in HF patients with severe SDB. These results suggest that autonomic nervous disintegrity may relate to adverse prognosis across a 24-hour period in HF with SDB.

P5306 | BENCH
Effects of acute and repetitive obstructive respiratory events on ventricular repolarization in a pig model for obstructive sleep apnea

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Introduction: Obstructive sleep apnea (OSA) is associated with sudden cardiac death. Obstructive respiratory events, as occuring in OSA, are associated with negative intrathoracic pressure, which may disturb ventricular repolarization resulting in arrhythmias.
Methods: In a pig model for OSA, indices of ventricular repolarization (QT-intervals) and dispersion of repolarization (Tpeak to Tend (TpTe), TpTe/QT ratio) were determined during and after repetitive tracheal occlusions with applied negative thorathic pressure (OSA-maneuver) for 3 hours (n=7). 5 animals without OSA-maneuvers served as a control.
Results: 2 minutes of acute OSA-maneuver resulted in negative thoracic pressure, pronounced hypoxia and hypercapnia and was associated with a non-significant shortening in RR-interval (769±84 ms to 722±115 ms, p=0.11). QT-interval was shortened (from 468.8±39.8 ms to 442.9±73.5 ms, $p<0.05$) whereas TpTe was prolonged (from 48.7±10.6 ms to 59.9±10.8 ms, $p<0.01$) and the TpTe/QT ratio was increased from 0.09±0.01 to 0.12±0.02 ($p<0.01$). Additionally, repetitive obstructive respiratory events over 3 hours caused a prolongation of QT from 426.5±47.0 ms at baseline to 474.4±59.2 ms (p=0.007), but TpTe was not significantly different, when measured during normal breathing. This QT-prolongation was not observed in animals without OSA-maneuvers.
Conclusion: Acute and chronic application of obstructive respiratory events influence ventricular repolarisation and dispersion in repolarisation differently. Increased dispersion in ventricular repolarisation during acute OSA-maneuvers as well pronounced QT-prolongation after repetitive OSA-maneuvers may represent mechanisms for increased ventricular arrhythmias and sudden cardiac death in OSA.

P5307 | BEDSIDE
Utility of a Lewis lead for distinguishing atrioventricular re-entrant tachycardia from atrioventricular nodal re-entrant tachycardia

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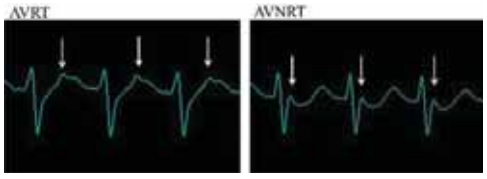
Purpose: A Lewis lead configuration can help to detect atrial activity. We investigated the utility of a Lewis lead to distinguish orthodromic atrioventricular re-entrant tachycardias (AVRTs) through accessory pathways from typical atrioventricular nodal re-entrant tachycardias (AVNRTs).
Methods and results: Thirty consecutive patients (17 male, 59±14 year-old) with narrow QRS tachycardia documented on the electrocardiogram (ECG) who had an electrophysiology study (EPS) between July 1, 2012 and February 1, 2014 were included in this study. A Lewis lead, which is a bipolar chest lead with the electrode on the right aspect of the sternum at the second intercostal space instead of the right arm and the electrode on the fourth intercostal space instead of the left arm, were recorded during tachycardias. Ten patients were diagnosed with AVRTs and 20 patients with typical AVNRTs on EPS. In 6 of 10 patients with AVRTs, the positive P wave can be seen in lead I with the Lewis lead configuration and in 14 of 20 patients with AVNRTs. The RP interval of AVRTs was significantly longer than those of AVNRTs (86±17msec vs. 164±22msec, $P<0.001$).



ECG with the Lewis lead showing P wave.

Conclusions: A Lewis lead configuration may help to make difficult differential diagnosis among the re-entrant supraventricular tachycardias, owing to its ability to locate P waves.

TECHNICAL ASPECTS OF ATRIAL FIBRILLATION ABLATION

P5309 | BEDSIDE
A comprehensive approach to persistent atrial fibrillation: percutaneous MAZE-like electrical left atrial appendage isolation followed by LAA closure

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Purpose: The optimal ablation strategy for patients (Pts) with atrial tachyarrhythmias (ATa) despite of permanent PV isolation is controversial. Aside from rotor ablation and left atrial substrate modification electrical let atrial appendage (LAA) isolation (I) was discussed. The latter, however, is associated with increased risk of LAA thrombus formation. We therefore aimed to investigate the concept of percutaneous electrical LAAI followed by LAA closure (C).
Methods: Pts with ATa non responsive to PVI underwent a MAZE-like ablation procedure with the goal of LAAI. An electroanatomical mapping system and an irrigated 3.5mm tip catheter were used. By creating a septal-anterior line, a roof line and a mitral isthmus line LAAI was achieved, confirmed by a spiral catheter in the LAA (Fig. 1). The patients continued oral anticoagulation therapy (Group A) or underwent LAAC after 6 weeks (Group B). Follow up included ambulatory Holter monitoring and office visits.

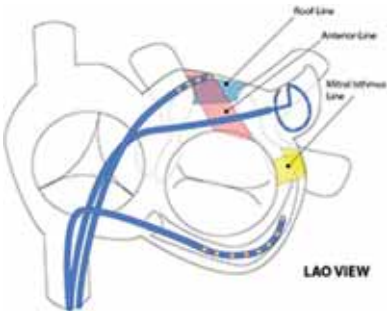

Figure 1

Results: Between June 2010 and February 2014, complete LAAI was performed in 45 pts (25 Male, 68±10 years; procedure time 134±44 min, fluoro time 16±7 min). In 3/45 (6,6%) pts cardiac tamponade occurred (managed conservatively). 16/45 (35%) patients received a LAAC (Group B) without major procedural complications. During a mean follow up of 336±240 days, 33% of pts. experienced a documented AF recurrence after the blanking period. In Group-A bleeding (1 pt) and thromboembolism (2 pts) were observed. No adverse events were noted in Group B.
Conclusion: Percutaneous MAZE-like procedures resulting in LAAI followed by interventional LAAC may be a favourable comprehensive approach to lower the risk for both, AF recurrence and thromboembolism. However, complex ablation increases the risk for cardiac tamponade.

P5310 | BEDSIDE
Evaluation of periesophageal nerve injury after pulmonary vein isolation using the 13C-acetate breath test

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Purpose: Pulmonary vein isolation (PVI) has become an important option for treating patients with atrial fibrillation (AF). Periesophageal nerve (PEN) injury after PVI causes pyloric spasms and gastric hypomotility. This study aimed to clarify the impact of PVI on gastric motility and assess the prevalence of gastric hypomotility after PVI.
Methods: Thirty consecutive patients with AF underwent PVI under luminal esophageal temperature (LET) monitoring. The 13C-acetate breath test was conducted before and after the procedure for all patients (PVI group). Gastric emptying was evaluated using the time to peak concentration of 13CO2 (Tmax). The test was also conducted in another 20 patients who underwent catheter ablation procedures other than PVI (control group).
Results: The number of patients with abnormal Tmax (>60 min) increased from 7 (23%) to 13 (43%) and from 3 (15%) to 5 (25%) after the procedure in the PVI group and control group, respectively. The mean Tmax was longer after PVI than before PVI (64±14 min vs. 57±15 min, P=0.006), whereas there was no significant difference before and after the procedure in the control group. However, no significant difference in ΔTmax was observed between the two groups (P=0.27). No patient suffered from symptomatic gastric hypomotility.
Conclusions: Asymptomatic gastric hypomotility occurred most frequently after PVI. However, the average impact of PVI on gastric motility under monitoring of LET was minimal.

P5311 | BEDSIDE

Residual conduction gaps after the first round of circumferential pulmonary vein isolation predict early pulmonary vein reconnection even after additional ablation

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Background: Circumferential pulmonary vein isolation (CPVI) is widely accepted for drug refractory atrial fibrillation (AF) and electrical disconnection of PV is the key concept of CPVI. Insufficient ablation at the first round of CPVI creates residual conduction gaps that require additional ablation, and we assume that the gap is a predictor of early PV recurrence (EPVR) during the procedure. The aim of this study is to evaluate the relationship between the residual PV conduction gap and EPVR.
Methods: We enrolled 110 paroxysmal AF patients underwent CPVI. After the first round of CPVI, additional ablation was applied to the conduction gap on the CPVI line if ipsilateral PV (iPV) was not isolated. EPVR was provoked by both time- and ATP-induction just after CPVI, 30, and 60min. We classified ipsilateral PV perimeter into 8 segments and evaluated the relationship between the segments of residual PV conduction gap after the first round of CPVI and EPVR during the procedure.
Results: 136/220 (61.8%) of iPV were isolated after the first round of CPVI, and 84/220 iPV (210/1760 segments) were required additional ablation to achieve complete PV isolation. EPVR were observed in 23/220 iPV (27/1760 segments), 40/220 iPV (67/1760 segments) and 4/152 iPV (7/1216 segments) just after CPVI, 30 min and 60 min respectively. Residual conduction gap predicts EPVR just after CVI, 30min, and 60min (HR=4.49 ($P<0.001$), 6.13 ($P<0.001$), and 4.79 ($P=0.04$), respectively).
Conclusion: Residual PV connection gap after the first round of CPVI is a strong predictor of EPVR even after additional ablation.

P5312 | BEDSIDE

Efficacy of a single hybrid ablation procedure in patients with long standing persisting atrial fibrillation in comparison to a standard endocardial approach: two years results

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Introduction: Unfortunately the success rate of catheter ablation of long standing persisting atrial fibrillation (LSPAF) remains poor even after multiple ablation procedures. Combining epicardial and endocardial approach (hybrid ablation) we could show a success rate of 76% one year after ablation. The objective of this study was to compare the efficacy of hybrid ablation with the standard endocardial, 3D-guided ablation in patients (pts) with LSPAF.
Methods: For this purpose pts with LSPAF, ablated using hybrid approach (group 1) were matched to those after conventional, 3D-guided radiofrequency ablation (group 2). The end point of this study was a number of pts free of any atrial arrhythmia >30 seconds at 24 month follow up (FU) after a single procedure in each group. In group 1 epicardial ablation was first performed via an endoscopic subxyphoid access utilizing Numeris® Coagulation Device. It was secondly followed during the same day by endocardial ablation utilizing EnSite NavX Velocity™ system. During this endocardial part voltage mapping was performed, detected gaps closed and additional linear and/or CFAEs ablations applied as needed. In group 2 conventional endocardial procedure was performed using EnSite NavX Velocity™ system. After completion of wide area circumferential ablation a step-up protocol was applied, aiming conversion into SR during ablation. Pts in group 1 were prospectively followed at 1, 2, 3 months with 48 h holter ECG and every 3 months thereafter. Pts free of AF after 3 months underwent implantation of loop event recorder, Reveal™, Medtronic Inc. Pts in group 2 were prospectively followed every 3 months with 72 h holter ECG.
Results: In each group 26 pts were included. Clinical and demographical characteristics between these groups did not differ but age (2 female, age 53±1 vs 59±2 years, p=0.042, LA area 28±0.7 vs 27±1 cm^2, p=ns in group 1 and 2 respectively). AF was persisting since 50±8 months and 19±4 months after last cardioversion attempted (group 1) vs 49±10 and 17±3 months (group 2), p=ns. 10 pts (39%) in each group have already undergone repeated AF catheter ablations. All pts were highly symptomatic with EHRA class 4. After a median follow up of 588 (IQR 407-795) days 19 (73%) pts in group 1 and 8 (31%) in group 2 were free of AF/AT without AADs ($p<0.01$).
Conclusions: A single hybrid ablation of LSPAF in pts with severe atrial enlargement represents a much more effective treatment modality as compared to a standard endocardial approach. Further evaluation of long-term results is required.

P5313 | BEDSIDE

Left atrial fibrosis is a predictor for outcome after Cryoballon ablation in patients with paroxysmal atrial fibrillation - lessons learned from LGE-MRI

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Background: Cryoballoon ablation is an alternative energy source for pulmonary vein isolation (PVI) in patients with paroxysmal atrial fibrillation (PAF).
Methods and result: Eighty-three patients with PAF (53 male, mean age 61.2±10.6 years old) were included into this study. All patients underwent LGE-MRI to quantify the degree of left atrial fibrosis (LAF). Based on the degree of LAF patients were stage into two groups: in patients with early stages of LAF (e.g. <20% of the LA, Utah Stage 1 & 2, Group A) and in patients with progressed stages of LAF (>20% of the LA, Utah 3&4, Group B). 52 (62.7%) patients were staged in Group A, while 31 patients (37.3%) were stage in Group B (Figure 1,blue columns). A total of 14 patients (16.87%) were found with recurrent AFIB 90 days after ablation. Success rate at 3 months after PVI was significant better in patients with early stages of structural remodeling of LA (90.38% vs 70.97%, p=0.022; Fig. 1, red columns). Degree of LAF detected using LGE-MRI was significant higher in patients with recurrence (21.97%±8.6% vs. 16.68%±7.42%; p=0.021, Fig. 2).

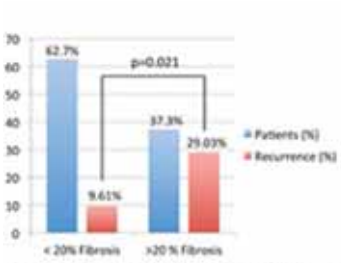

Figure 1: % of patients with varying stages of LA-SRM (> or < 20% of LA SRM, blue columns). Red columns gives % of patients with recurrence AFIB at 3 months after ablation in each group).

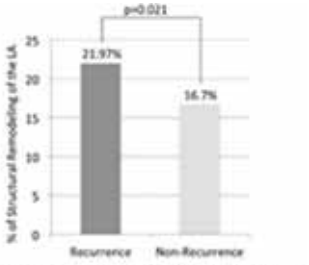

Figure 2: % of Left Atrium Structural Remodeling in patients with (left columns) and without reccurent atrial fibrillation (right columns) 3 months after pulmonary vein isolation).

Conclusion: From our preliminary results the degree of left atrial fibrosis detected using LGE-MRI predicts success rates for Cryoballoon-Ablation in patients with paroxysmal atrial fibrillation. As patients with paroxysmal AF can show varying degrees of fibrosis, LGE-MRI for assessment of the degree of LAF might be able to support the choice of the adequate energy source for PVI in these patients.

P5314 | BEDSIDE

Pulmonary vein isolation using a visually guided laser balloon catheter in a spanish center

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Novel catheter designed to facilitate atrial fibrillation (AF) ablation include a visually guided laser ablation (VGLA) catheter that allows the operator to directly visualize target tissue for ablation and then deliver laser energy to perform point-to-point circumferential ablation. The aim of our study was to describe the initial experience with VGLA at our center, the first in Spain to use this technique, and to compare these results with ablation with radiofrequency also at our center.
Method: We collected: patient demographics, pulmonary vein (PV) anatomy (PVA), procedure time (PT), fluoroscopy time (FT), procedure success (PS) defined as isolation of all PV, % of isolated veins of targeted veins, % of isolated veins in the first attempt, isolation time of each pulmonary vein, % of patients with single crown of ipsilateral veins, number of ablation lesions per patient and periprocedural complications (C).
Results: 32 patients, 25% women, medium age 54±11 years, 81% paroxysmal AF.
PVA was normal in 81.3%, left common vein in 12.5% and right common vein in 6.3%. Using the VGLA catheter, 96.6% of targeted PVs were isolated, 91% of them after the first encircling lesion set. In 25% of patients a single crown of ipsilateral veins was made. In 90.6% of patients, isolation of all veins with the VGLA Catheter was achieved. PF and PT were 43±15 (mean±SD) and 156±30 minutes, respectively. There was a 3.1% incidence of cardiac tamponade and a 9.4% of femoral hematoma that did not require surgery. There was a 12.5% incidence of asymptomatic phrenic nerve injury, diagnosed as elevated right hemidiaphragm in the radiological control.
There were no statystically differences in PS compared with radiofrequency, with less PT (156 vs 184; p=0.04) in laser ablation group but without statystically differences FT.
Conclusions: Pulmonary vein isolation using a VGLA catheter is a novel technique recently introduced in our center and our country. The efficacy is similar to other AF ablation technologies (with a 96.6% of targeted PVs isolated). It is reasonably safe, but it remains a rate of 3.1% of pericardial tamponade and 12.5% of asymptomatic phrenic nerve injury.

P5315 | BEDSIDE

Additional linear ablation from superior vena cava to right atrial septum after pulmonary vein isolation improves clinical outcome in patients with paroxysmal atrial fibrillation

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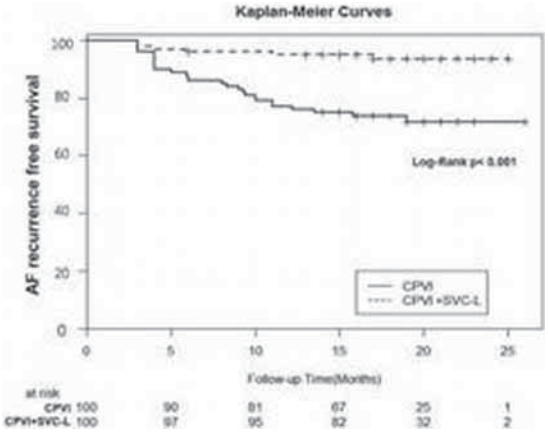
Purpose: Although circumferential pulmonary vein isolation (CPVI) has been considered as the cornerstone for paroxysmal atrial fibrillation (PAF) ablation, there has substantial recurrence rate. We conducted prospectively randomized study to evaluate whether the additional linear ablation from superior vena cave (SVC) to right atrial (RA) septum (SVC-L) improves clinical outcome.
Methods: This study enrolled 200 patients with PAF (male 74.5%, 56.8±11.7 years old) and randomly assigned to CPVI (n=100) and CPVI +SVC-L groups (n=100). RA isthmus block was done in all patients. CPVI+SVC-L group required longer procedure ablation time (4959±1074 sec) than CPVI group (3814±1009 sec, $p<0.001$). Complication rates were not significantly different between CPVI+SVC-L (5%) and CPVI group (2%, p=0.445). There were 2 post-procedural sinus node dysfunction those recovered within 24 hours in CPVI+SVC-L group.
Results: During 12.2±5.3 month follow-up, the clinical recurrence rate was significantly lower in CPVI+SVC-L group (6%) than in CPVI group (27%, $p<0.001$). Post-procedural 3 month follow-up heart rate variability showed more significant reductions of rMSSD (25.2±13.7 vs. 13.7±8.5ms, $p<0.001$), HF (10.2±7.1 vs. 5.5±5.8ms2, $p<0.001$) and LF/HF (1.6±0.5 vs. 0.9±0.3, $p<0.001$) in CPVI+SVC-L group than in CPVI group.



KM curve comparing bewteen two group.

Conclusion: In spite of longer procedure time and risk of transient sinus node dysfunction, SVC-L in addition to CPVI improves clinical outcome of catheter ablation, associated with post-procedural autonomic neural remodeling in patients with PAF.

P5316 | BEDSIDE

Single-center experience with a novel multipolar ablation device for pulmonary vein isolation

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Background: We report on the initial experience with a novel single device circular irrigated radiofrequency (RF) ablation catheter.
Methods: 19 patients (60±14 years) with paroxysmal (8) and persistent (11) AF underwent pulmonary vein isolation (PVI) by using a novel decapolar mapping and ablation catheter between June and December 2013. Ablation was guided by electroanatomical mapping and RF energy was delivered in the antral region of pulmonary veins (PV) with any or all of the 10 irrigated catheter electrodes. Patient baseline and procedural caracteristics were documented and a follow-up (F/U) was performed by questionnaire or telephone interview.
Results: Overall, 66/74 targeted PV (89%; 1 patient with unsuccessful cardioversion, PVI could not be proved) could be isolated within a mean procedure time of 150±34 minutes and a mean RF delivery time of 969±323 seconds per patient. Total fluoroscopy time was 15,5±3,9 minutes with a dose of 2.465±2.869 $cGycm^2$. No procedure-related complications were observed. During F/U (1-7 months) 2 patients (11%) (1 paroxysmal, 1 persistent) were in SR without antiarrhythmic drugs (AADs), 11 patients (58%) (4 paroxysmal, 7 persistent) in SR with AADs and 6 patients (32%) (3 paroxysmal, 3 persistent) had a relapse of AF. In a questionnaire (11) or a telephone interview (5) 8 patients reported their overall health condition to be “much better”, 6 patients “slightly better” after PVI than before, and 2 patients reported “no change”.
Conclusion: PVI using the novel irrigated RF multipolar ablation device requiring only 1 transseptal puncture appears to be acutely effective. No clinical complications were identified. The short term efficacy seems to be comparable to established ablation tools and strategies, but long term efficacy and F/U trials are needed.

P5317

ABSTRACT WITHDRAWN

P5318 | BEDSIDE

Atrial fibrillation termination caused by pulmonary vein isolation prior to complex fractionated atrial electrograms guided ablation

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Background: Whether there is correlation of atrial fibrillation (AF) termination during ablation and good outcome or not is still controversial based on pulmonary vein isolation (PVI) combined with other anatomical and/or electrogram guided ablation. Then we analyzed how often AF termination was caused by pulmonary vein isolation (PVI) prior to complex fractionated atrial electrogram (CFAE) guided ablation, and how predictable the AF termination by PVI in the good outcome.
Methods and results: This study included 132 consecutive patients (81 paroxysmal/51 persistent AF, mean age of 60 years old) who underwent AF ablation combined with ipsilateral PVI during AF spontaneously or by induction prior to CFAE ablation. Six patients to be achieved PVI during sinus rhythm, because AF could be maintained only with isoproterenol infusion, were excluded to analyze the AF termination caused by PVI. In the rest of 125 patients, 86 (55 paroxysmal/31 persistent) were their first session, and 39 (19 paroxysmal/20 persistent) had a history of AF ablation solely guided by CFAE. In the 125 patients, PVI during AF caused AF termination 45% in paroxysmal and 20% in persistent; 36% and 13% in the patients of their first session, and 68% and 30% in the patients had a history of CFAE ablation, respectively. AF was not inducible in 4 paroxysmal patients of their first session and 2 persistent patients had a history of CFAE ablation. AF was terminated 92% of paroxysmal and 70% persistent AF combined with CFAE ablation. There were no difference in the total RF duration between the AF-termination group (96 min) and non AF-termination group (96 min). AF termination was caused by the ablation of the electrograms of the ablation catheter showed CFAE in 67%. AF termination was caused by mean of 46% of RF points achieved the PVI in the RF site of PV. PVI was confirmed with a circular catheter and completed electrically in the end of the session. The recurrence rate in the patients with or without AF termination by PVI were 56% (59% of PAF, 50% persistent) and 47% (41% of PAF, 56% with persistent) with mean of 21 months follow up.
Conclusion: AF termination by PVI is not a predictor of AF recurrence in PVI combined with CFAE ablation. PVI during AF is not favorable to assume their outcome.

OUTCOME IN ATRIAL FIBRILLATION ABLATION

P5320 | SPOTLIGHT
The impact of atrial fibrillation termination mode during catheter ablation procedure on maintenance of sinus rhythm

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Background: Catheter ablation is a common and effective procedure to address atrial fibrillation (AF) refractory to antiarrhythmic drugs. AF can be terminated directly into sinus rhythm (SR); evolving into regular atrial tachycardia (AT) and subsequently into SR; after direct current (DC) cardioversion if AF persists. Scarce data are available on the relationship between clinical outcomes and termination mode after one catheter ablation. We evaluated for the first time the association between 1-year ablation efficacy and termination mode after repeated catheter ablations.
Methods and results: This prospective study involved 400 consecutive patients (62.7±7.2y) who underwent catheter ablation for drug-refractory persistent AF (4.6±2.4 months) using a stepwise ablation approach.
AF was terminated by radiofrequency application directly into SR in 135 patients; passing through AT into SR in 195 patients; through DC cardioversion in 70 patients. After 1 year of follow-up with repeated Holter monitoring, the percentages of SR maintenance were, respectively, 72.6%, 80.0% and 28.6% ($p<0.001$). As compared with the subjects who were converted directly into SR, the adjusted hazard ratios (HRs) of SR maintenance were significantly lower for those who required DC cardioversion (HR=0.54; $p<0.001$); higher for those converted through AT (HR=1.69; p=0.027). The latter association was even stronger in the 104 subjects who required a second procedure (HR=6.25; p=0.001).
Conclusions: Termination of AF after AT during catheter ablation is associated with a lower likelihood of AF/AT recurrence at 1 year after both the first and second procedure.

P5321 | BEDSIDE
Efficacy and safety of left anterior ridge and carina first ablation to prevent esophageal complications in patients with atrial fibrillation

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Purpose: Severe esophageal complications such as gastric hypo-motility or left atrial-esophageal fistula after catheter ablation (CA) for patients with atrial fibrillation (AF) have been reported. Esophageal temperature (EST) monitoring may be a useful tool to know the temperature inside the esophagus during left atrial posterior wall (LAPW) ablation. However, its efficacy for preventing gastric hypomotility which must be caused by vagal nerve injury outside the esophagus is not well known. The objective of this study was to evaluate the efficacy and safety of left anterior ridge and carina first ablation to minimize the left atrial posterior wall ablation near the esophagus for pulmonary vein isolation.
Methods: Consecutive 86 patients with AF (61±10 years, 64 males, 58 paroxysmal AF) underwent CA with esophageal temperature (EST) limiting <39 degrees were studied. Intensive ablation for anterior ridge and carina of left pulmonary veins (LPV) followed by electrically guided LAPW ablation for LPV isolation was performed in 23 patients (Minimized-PVI group). Extensive encircling LPV isolation was performed in other 63 patients (EEPVI group). Right PVs were encircled in both groups. The procedure results and clinical outcome were compared.
Results: Left PVs were isolated only by carina and ridge ablation without EST>39 degrees in 12 patients of Minimized-PVI group (52%). Total number of LAPW ablation sites (2.1±2.5 vs. 12±3.3, $p<0.001$), EST>39 degrees (0.7±1.3 vs. 4.8±3.8, $p<0.001$) and ablation for LPV isolation (22±5.5 vs. 35±10, $p<0.001$) were lower in the Minimized-PVI group. Incidence of AF triggering extra-PV foci under isoproterenol infusion was similar in both groups (13% vs. 14%) and these were treated with additional ablation for extra-PV foci or left atrial posterior box isolation. Symptomatic gastric hypo-motility occurred in 1 patient of EEPVI group with nine ablation sites including EST had reached 39 degrees three times at LAPW for LPV isolation. In patients with paroxysmal AF, 81% (13/16) of Minimized-PVI group and 74% (31/42) of EEPVI group were free from AF at 6 months follow-up.
Conclusion: Left anterior ridge and carina first ablation to minimize LAPW ablation near the esophagus must be a useful strategy for LPV isolation to reduce the potential risk of esophageal complications without increasing the AF recurrence.

P5322 | BEDSIDE
Absence of changes in pulmonary vein activation sequence during cryoablation indicates a homogeneous lesion

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Background: Changes in the pulmonary vein (PV) activation sequence (AS) are frequently seen during radiofrequency guided atrial fibrillation (AF) ablation. Our purpose was to determine the PV potential (PVP) AS during cryoablation.
Methods: The recordings of 55 patients who underwent PV disconnection by cryocatheter were reviewed. After transseptal puncture, a 23mm or 28mm cryoballoon along with a multipolar catheter was inserted into the left atrium. After recording PVP the balloon was positioned at the antrum of each PV. Contrast was injected to assess the exact position. The multipolar catheter was positioned as proximal as possible to provide PV recording. A distal position where PVP could not be visualized was required when balloon support was inadequate. PVP sequence was defined when at least 3 non-consecutive poles showed PVP (i.e. non consecutive activation) indicating at least two muscular strands. If PV potentials visualization during freezing was not possible, PV remap was performed at the ostium after the freeze.
Results: A total of 224 PVs were analyzed. Eleven of the 224 PVs (5%) were basally isolated. In 82 PVs (36.5%), PVP could not be recorded during ablation (2 PVs showing only 2 non-consecutive PVP where included in this group). Forty-nine PVs (22%) were in AF and were excluded from analysis. Therefore, AS was analyzed in 82 PVs (36.5%). One vein could not be isolated; of the remainder 81 PVs the AS was unchanged in all before isolation: the pattern of isolation was sudden in 30 (13%), after a 2:1 block period in 12 (5%) and after a progressively delay in 39 (17%). Fig 1.

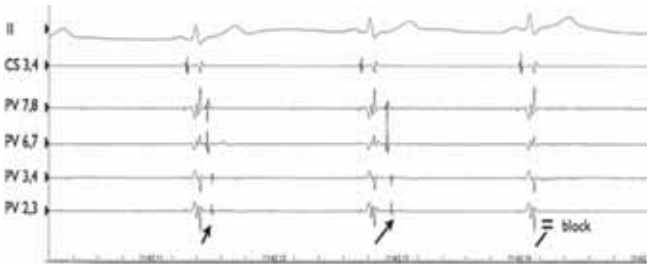

Figure 1. Disconnection sequence.

Conclusions: During a cryoablation procedure, the absence of changes in the PV AS after a conduction delay suggests that this energy produces a very homogeneous lesion.

P5323 | BEDSIDE
Poor recovery of left atrial appendage volume after successful ablation therapy for persistent or chronic atrial fibrillation

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Purpose: Recovery of left atrial size, i.e. negative remodeling of the left atrium (LA), after catheter ablation of persistent or chronic atrial fibrillation was reported. Morphological change of LA after ablation therapy, however, has not been precisely described. We studied morphological change of LA and LA appendage (LAAV) after successful ablation of persistent or chronic atrial fibrillation using cardiac CT.
Methods: Cardiac CT was performed using Light Speed VCT in seventy patients with persistent or chronic atrial fibrillation before and after successful ablation. Second examination of cardiac CT was performed 100±36 days after the ablation. LA volume was measure by the method of discs (0.625 mm thick) and 3D reconstruction. Total LA volume (LAVtotal) was divided into two volumes: LA body without appendage (LAVbody) and LA appendage (LAAV). LA diameter was measured in three orthogonal axes (X=anterior to posterior diameter, Y=right to left diameter, Z=top to bottom diameter). Measurements were duplicated by two experienced researchers in blind manner.
Results: LAVtotal reduced from 157±35 to 114±29 ml, and LAVbody also reduced from 145±34 to 100±27 ml, significantly. LAAV, however, was not changed (before:12.2±4.6, after:13.3±7.2 ml). Diameters in all three axes were reduced: X from 39±6.8 to 34±6.5 mm, Y from 62±8.5 to 54±7.8 mm, Z from 66±6.7 to 55±7.1 mm, and the reduction was statistically significant.
Conclusions: Negative remodeling of LA was observed after successful ablation of persistent or chronic atrial fibrillation; however, recovery in the size of the LA appendage was not observed within 100 days after successful ablation therapy. This might be a possible cause of thromboembolic complication after ablation therapy.

P5324 | BEDSIDE
Reduction of cardiac tamponades in AF ablation using balloon technologies

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Purpose: The major cause of death during catheter ablation of atrial fibrillation (AF) is related to cardiac tamponade (CT). The risk of CT may be linked to different procedural steps such as transseptal puncture (TP), catheter manipulation during left atrial (LA) and pulmonary vein (PV) mapping and ablation.

Methods: All AF ablation procedures performed in our center between May 2010 until November 2013 have been reviewed. Two groups were defined: group A: radiofrequency current (RFC) ablation, group B: balloon ablation. Group A: 2 TPs were performed followed by wide area circumferential point-by-point PV isolation (index procedure) within a 3D LA map (CARTO, NAVX) and CFAE and/or linear lesions (redo-procedure). Group B: 1TP followed by balloon based PV isolation (cryoballoon (CB), laserballoon (LB)). All CTs were analyzed with regards to procedural characteristics, energy source and CT management.
Results: A total of 1763 AF ablation procedures have been performed in our institution. Group A: n=1212; (index procedure: n=887, re-procedures: n=325), group B: n=551 (CB: n=354 + LB: n=197). Overall, the grand total rate of CT was 1.2% (21/1763). The rate of CT was significantly lower in group B compared to group A: 0.18% (1/551) vs. 1.7% (20/1212) (p=0.007). The single CT in group B was caused by the historical stiff nose of the first generation LB while PV mapping. In group A, the risk of CT during the index PV isolation procedure was significantly decreased compared to re-procedures including complex ablation: 1.0% (9/887) vs. 3.1% (10/325) (p=0.018). The vast majority of patients 95% (20/21) experiencing CT could be managed without surgery after drainage of median 500 ml (Q1-Q3: 300-800ml) blood.
Conclusions: Cardiac tamponade is a very rare complication following balloon based AF ablation. The risk of cardiac tamponade is increased in RFC ablation, especially if extensive ablation beyond PV isolation is performed.

P5325 | BEDSIDE
Pulmonary vein isolation with a new multipolar irrigated radiofrequency ablation catheter: feasibility, efficacy and safety

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Purpose: Simultaneous multipolar ablation catheters for pulmonary vein isolation (PVI) have been proposed in order to simplify the atrial fibrillation (AF) ablation procedure. A new multipolar circular open-irrigated radiofrequency ablation catheter (nMARQTM) combining both mapping and multi-ablation capability through open-irrigation design has recently been developed. Our study aims to assess the feasibility, the acute success and the safety of this new technology with a particular interest in the incidence of periprocedural silent cerebral lesions (SCL) in patients undergoing AF ablation.
Methods: 29 patients (age 55±14 years) with paroxysmal AF underwent PVI using the nMARQTM catheter. PVI was confirmed by circular multipolar mapping catheter (Lasso). A cerebral magnetic resonance imaging (MRI) was performed before and after the procedure.
Results: The ablation procedure with the nMARQTM was feasible in all the patients without the use of a steerable sheath. PVI was achieved in 98% (117/119) of pulmonary veins identified and in 96% (28/29) of patients treated. Mean procedural time was 128±50 min, while mean fluoroscopy time was 1.7±2 min. Mean total RF time was 15.3 min. Out of 29 procedures, no procedural complications, including SCL, occurred.
Conclusions: In our experience, PVI with nMARQTM catheter was feasible with good acute success and safety profile. No procedural complications, including new SCL detected by post-ablation brain MRI, were reported.

P5326 | BEDSIDE
Disparate response of high frequency ganglionated plexus stimulation on sinus node function and atrial propagation in patients with atrial fibrillation

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Purpose: The autonomic nerve system plays an important role in triggering atrial fibrillation (AF), however little is known of its effect on atrial conduction characteristics in patients with AF. We studied the effect of high frequency anterior right ganglion plexus (ARGP) stimulation during sinus rhythm on the sinus node and the AV-node and the epicardial atrial conduction times and inhomogeneity of conduction of the right atrial (RA) or right pulmonary vein (RPV) myocardium in patients undergoing thoracoscopic surgery for AF.
Methods: In 25 patients with AF, the ARGP was stimulated using a stepwise stimulation protocol (16 Hz, at 1, 2 and 5mA). Epicardial electrograms were recorded using a custom made 6x8 electrode grid (interelectrode distance 1 mm) on the RPV or RA and intra-atrial (IAT), local activation time (LAT) and inhomogeneity of conduction (IIC) were determined and ECG parameters (P-P, P-R interval) were measured during sinus rhythm activation directly before and after stimulation.
Results: Mean age was 59 years and 17 patients were male. Fourteen patients had paroxysmal AF (56%) and 11 patients had persistent AF (44%). Thirteen underwent RA myocardial recordings and 12 PV myocardial recordings.
Baseline P-P interval was 956±157ms (range 768-1368ms) and P-R interval was 203±37ms (range 136-280ms). After ARGP stimulation, a short-lasting increase of P-P interval was observed, more prominent at higher output (1mA=82ms, 2mA=180ms, 5mA=268ms, all <0.01 vs baseline). P-R interval remained unchanged.
IAT was 34.4ms (range 5.6-50.3ms) at the RA and 105.8ms (range 79.7-163.3ms) at the RPV. After 1mA ARGP stimulation IAT increased in patients with beta-blockers (p=0.001), or decreased and this change persisted after subsequent stimulation at higher current (1mA p=0.001, 2mA p=ns, 5mA p=ns). Similar changes were observed for LAT and IIC.
Conclusion: ARGP stimulation results in a short-lasting, output-dependent, decrease in sinus node frequency, due to a parasympathetic response in patients with AF. Stimulation of the ARGP induced a prolonged increase or decrease in conduction characteristics, consistent with a persistent differential parasympathetic and/or sympathetic response. Patients with beta-blocking drugs predominantly showed an increase of IAT. These data supports the notion that GP activation may contribute to the arrhythmogenic substrate for AF, and that GP ablation is anti-arrhythmic, not only by preventing triggered activity, but by modulation of atrial conduction.

P5327 | BEDSIDE
Assessment of left atrial volume in patients with atrial fibrillation: a correspondence between echocardiography and 3D mapping

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Background: Left atrial (LA) enlargement is a predictor of worse outcome after catheter ablation (CA) for atrial fibrillation (AF). We investigated the correspondence between two LA volume (LAV) indices assessed by echocardiography (ECHO) and LAV obtained by 3D electroanatomic mapping (CARTO) in patients undergoing CA for AF.
Methods: We performed analysis in 816 pts (59±9 years; 66% males; 49% paroxysmal AF) from three ablation centres. ECHO LAV indices assessed by ellipsoid model (LAVE) and by biplane area-length method (LAVA) were compared with CARTO-derived LAV (LAV3D) by Pearson's correlation and modified Band-Altman method. LAV3D validated by CT image registration in a subset of patients was considered a gold standard.
Results: Mean LAVE was 69±24 ml, LAVA was 88±30 ml and LAV3D was 131±46 ml. Correlation between LAVE or LAVA and LAV3D was modest (r=0.70 and 0.56, respectively), and significant less tight for LAVA ($p<0.001$). LAVE and LAVA underestimated LAV3D with absolute bias (95% CI) of 64 ml (-2 – 130) and 57 ml (-17 – 131), and relative bias of 54% (24 – 83) and 63% (24 – 102); ($p<0.0001$ for their mutual difference), Fig. 1.

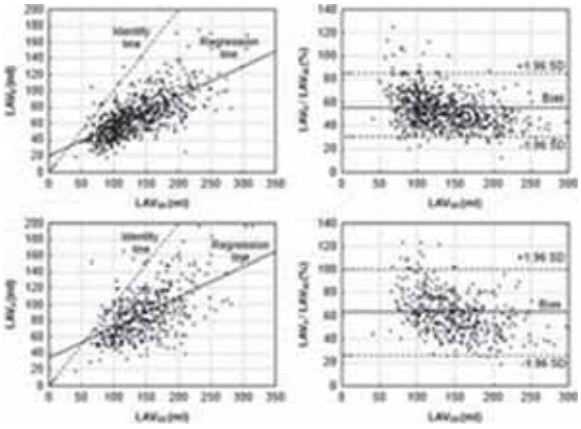

Figure 1

Conclusion: ECHO indices systematically underestimated CARTO-derived LA volume by ~ 40% so that the magnitude of absolute bias was greater for enlarged LA. LAVE compared to LAVA had lower accuracy but higher precision to quantify the true LAV.

P5328 | BEDSIDE
Evolution and management of acute and delayed reopening after the lariat endo epicardial closure

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Introduction: Thromboembolic events represent one of the most serious complication of atrial fibrillation. Left atrial appendage (LAA) clot is the dominant cause of stroke in AF patients. Therefore endocardial and epicardial LAA closure devices have been developed. We sought to evaluate the follow up and the management of incomplete acute closure and delayed reopening of the LAA after lariat endo epicardial ligation.
Methods: This was a multicenter study of consecutive patients undergoing LAA ligation for stroke prevention in atrial fibrillation. At implant successful ligation was defined as Lariat deployed with <5mm residual leak by trans-esophageal echocardiogram (TEE).
Results: A total of 75 patients were enrolled at 3 Institutions. There were no procedural deaths or strokes, and the rate of major bleeding was 9.3%. In one patient the device could not be deployed because of non favorable anatomy. Out of 74 Lariat cases, TEE complete follow up was available in 63 pts. Out of these in 58 pts no acute leak was measured, while a leak (<5mm) was detected in 5 pts at implant. At follow up, 3 of the 5 pts with a leak <5 mm had no leak and in 2 cases the leak stay unchanged. Out of the 58 pts with no leak at implant, 46 had no leak at follow up, 7 had a leak of less than 5 mm, and 5 developed a leak of more than 5 mm. In four of the 5 cases with a leak >5mm (1 cm in two cases) an endocardial closure device was placed to close the leak in the LAA. After closure all patients discontinued anticoagulation.
Conclusion: Our registry showed that 27% of patients have various degree of left atrial appendage leak after the lariat procedure. Most of these leaks can be successfully closed with smaller closure devices.

VENTRICULAR ARRHYTHMIAS

P5330 | BEDSIDE
Gender differences in the inheritance mode of RYR2 mutations in catecholaminergic polymorphic ventricular tachycardia patients

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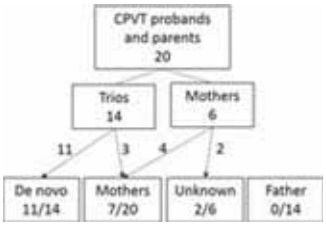
Purpose: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is one of the causes of sudden cardiac death in young people and resulted from RYR2 mutations in 60% of CPVT patients. This study aimed to elucidate the clinical aspects of CPVT depending on the inheritance pattern of RYR2 mutations.
Methods: Our study cohort consisted of 20 CPVT probands (8 boys) with RYR2 mutations and their parents; 14 sets of proband/both parents (trio) and 6 sets of proband/mother. We performed genotyping on their parents, examined the inheritance mode and evaluated the clinical characteristics of the probands.
Results: As shown in the figure, 11 mutations were de novo, and 3 were inherited from the maternal side, but none from the paternal side in 14 trios. In 6 patient/mother sets, 4 mutations were inherited from mothers and 2 were of unknown origin (i.e., either de novo or paternal side). In total, we found that 6 probands' RYR2 mutations came from mothers (6/20; 30%), while none from fathers (0/14). The RYR2 mutation inheritance is significantly higher from maternal than paternal side (P=0.026). Among 8 mutations identified in boys, 6 (75%) were de novo, while 5 de novos (41.7%) from 12 mutations identified in girls. The mean age of onset in de novo mutation carriers was younger (6.9±4.2 years) than that of mutation carriers inherited from mothers (10.7±3.0 years), though there was no statistical significance (P=0.053).



Inheritance pattern of RYR2 mutations.

Conclusions: More than half of the RYR2 mutations identified in CPVT probands were de novo, and others were mainly inherited from their mothers. These findings may indicate that male CPVT patients had premature arrhythmic death before the introduction of flecainide as a therapeutic strategy.

P5331 | BEDSIDE
Arrhythmia risk stratification patients with dilated cardiomyopathy for primary prophylactic

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Arrhythmia risk stratification with regard to prophylactic implantable cardioverter-defibrillator (ICD) therapy is a completely unsolved issue.
Purpose: This study was designed to determinate a potential noninvasive arrhythmia risk predictors in patients (pts) with dilated cardiomyopathy (DCM)
Methods: The study enrolled 234 pts with idiopathic DCM and ischemic DCM. Arrhythmia risk stratification was performed prospectively during 39±7 months of follow-up, including analysis of left ventricular ejection fraction (LV EF) and size by echocardiography, QTc dispersion, heart rate turbulence (HRT) and microvolt T-wave alternans (mTWA). Also we analyzed age, gender, NYHA, 6-MWT, BNP level and data of 24h-Holter ECG (nsVT, PV ectopy). Arrhythmic events were defined as sustained VT, VF, sudden death, resuscitation or ICD discharges.
Results: By multivariate regression analysis, with multipliers of determination R=0,70; F=30,8: positive mTWA (p=0,000), LV end-diastolic diameter (p=0,015) and QTc dispersion (p=0,027) were detected as independent risk predictors in pts with sinus rhythm only. Unfortunately, HRT (TS) value has been beta 0,35 (p=0,049). Thus, for risk estimate of fatal arrhythmic events (in pts with sinus rhythm) classification formula is presenting:
AR (≤1) = -0,01 x mTWA + -0,009 x LVendDD + -0,002 x QTd.
In pts with atrial fibrillation (AF) multivariate regression analysis also identified QTc dispersion (p=0,004), gender (p=0,018) and LV ejection fraction (p=0,000) as significant risk predictor with multipliers of determination R=0,93; F=12,9. So, for pts with AF formula separating is looks:
AR (≤1) = 0,035 x LV EF + 0,36 x gender (1 male, 0 female) + -0,005 x QTd.
Conclusion: Formula's estimate may be helpful for arrhythmia risk stratification and screening should be performed in pts with DCM as potential candidates for prophylactic ICD therapy. Result of this study provide useful information regarding the design of future studies evaluating the benefit of prophylactic ICD therapy in pts with DCM.

P5332 | SPOTLIGHT
Lay as first responders in the treatment of ventricular fibrillation: doubled survival rate in Piacenza "Progetto Vita" (PV) from 1999 to 2013

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The system of early defibrillation called "Progetto Vita" (PV) was organized within a traditional Emergency Medical System (ACLS-ambulance) and ambulance of volunteers (BLS-ambulance). Lay volunteers were trained to use only the automated external defibrillator (AED) (PV-AED) without performing Cardio-Pulmonary Resuscitation (BLS).
Objective: To evaluate survival rate from out-of-hospital cardiac arrest and ventricular fibrillation (VF) in this early defibrillation program in patient treated by ACLS or BLS ambulance and by lay volunteers.
Methods: A retrospective observational design has been used to investigate the survival rate on out-of-hospital sudden cardiac arrest (SCA) therapy organized in the Italian city of Piacenza, in which police and lay volunteers are trained to use automated external defibrillators (AEDs)
Data were collected with the use of a database according to the Ulstein-style for all cases of out of hospital cardiac arrest from June 1999 to December 2013. Data collections include also the cardiac rhythm recorded by AED or monitor ECG and were divided into two groups, according to the type of first responder: ACLS-ambulance or BLS-ambulance in group 1, PV-AED in group 2.
STATISTICAL ANALYSIS
The sample will be described by means of the usual descriptive statistics: mean and standard deviation for continuous variables and proportions for categorical ones. To compare the survival rate from VF and SCA pts student's t-test for continuous variables, chi-square for categorical variables, or the correspondent non parametric tests will be used when appropriate.
Results: Among dispatched sudden cardiac arrest, (VF) was recorded as primary rhythm in 516/3832 pts (13,47%) with a total survival rate from VF of 134/516 (25,97%). In group 1 survival rate from VF was 22,15% vs 50,72% (p<0.0001) in group 2. From SCA, in group 1 survival rate from SCA was 3,21% vs 39,13% (p<0.0001) in group 2.
Conclusions: PV-AED only trained to defibrillate saved more pts in VF cardiac arrest than ACLS ambulance or BLS-ambulance. The extensive use of AED by lay volunteers saved up to 50,72% of VF cases that was almost doubled compared to ACLS-ambulance and BLS-ambulance. BLS training does not influence survival when AED is applied early after collapse.

P5333 | BEDSIDE

Chronic obstructive pulmonary disease is a risk factor for ventricular arrhythmias independent of left ventricular systolic function

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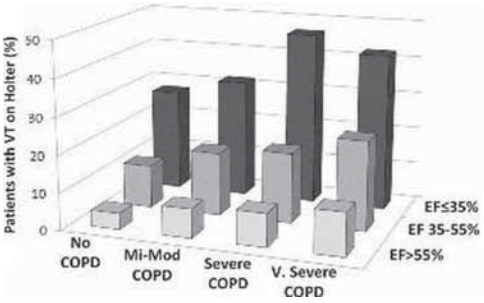
Background: Chronic obstructive pulmonary disease (COPD) is associated with increased cardiovascular morbidity and mortality, yet the exact pathophysiological links remain unclear. Whether the presence and severity of COPD is associated with ventricular tachycardia (VT) independent of the left ventricular ejection fraction (LVEF) remains unknown.
Methods: We identified consecutive adult patients who underwent pulmonary function testing, 24-hour Holter monitoring, and trans-thoracic echocardiography between 2000 and 2009. Demographic data as well as relevant co-morbidities were gathered from the electronic medical record, severity of COPD was classified according to the GOLD classification, VT diagnosed as ≥3 consecutive ventricular beats at a rate >100/minute.
Results: From 6350 patients who were included (age 66±15 years, 48% woman, 92% Caucasian, LVEF 59±12%) COPD was diagnosed in 2799 (44%). COPD was associated with a nearly two-fold increase in likelihood of VT occurring on the Holter monitor (6.9% vs 13.7%, p<0.001). The severity of COPD was also predictive of the risk of VT (12.2% vs. 16.7% vs. 20% for mild-moderate, severe, and very severe COPD, respectively; p<0.001). COPD and VT remained independently associated (p<0.001) after stratifying for LVEF (Figure), demographics, and co-morbidities (age, gender, tobacco use, obesity, hypertension, coronary artery disease, heart failure, diabetes, chronic kidney disease).



COPD and VT stratified by LVEF

Conclusions: COPD is associated with increased risk of VT, proportionate to severity and independent of the LVEF. This provides insight into the markedly increased cardiovascular morbidity of COPD patients, and further studies should explore which anti-arrhythmic strategies would best apply to the COPD patients.

P5334 | BEDSIDE

Impact of automated template matching during PVC ablation: results from a randomized controlled trial

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Introduction: Radiofrequency ablation (RFA) is an established treatment of symptomatic PVC. Commonly, subjective pace mapping (PM) and activation mapping (AM) in the presence of spontaneous ectopy are utilized. The automated template matching tool (ATM) of a commercially available EP recording system was shown to predict successful ablation sites but has not been studied in a randomized trial. We report an initial cohort of pts from an ongoing randomized trial.
Methods: Patients were randomized 2:1 to either ATM or conventional mapping. Mapping in the control group (CG) was guided by subjective PM and AM if spontaneous PVC were present. In the intervention group ATM was utilized for an objective assessment the paced morphology. A 3D geometry was obtained in all pts and an electro-anatomical map was acquired if sufficient PVC were present. Follow up (FU) was performed at 3 months post ablation and consisted of 24h Holter ECG and assessment of symptoms. Endpoints were acute ablation success, defined as cessation of PVC at the end of the procedure, and recurrence of PVC at FU.
Results: Fifty-seven pts (Age 54±16, LV-EF 56±12%) with a PVC burden of 20±13% in pre ablation Holter and 20±17 PVC/min at the start of the procedure were included. Thirty-six were randomized to ATM and 21 to CG. Ablation sites were: RVOT n=29 (52%), LVOT n=19 (34%), Great Cardiac Vein n=4 (7%) and Aortic Sinus n=4. There was no significant difference in baseline parameters or ablation site. Complications were: VF during RFA n=3, pericardial tamponade n=1 and AV-fistula n=1.
Acute ablation success was 44/57 (77%, CG 15/21 and 29/36 ATM group; p=ns). There were significantly less RF applications in the ATM group (8±5 vs 13±11; p=0.016). At FU, PVC burden was lower (0.9±2% vs 3.6±6% p=0.047) in the ATM group. Also, symptom based recurrence rate was lower in the ATM group (8/36, 22% vs 8/21, 38%) but did not reach significance.
Conclusions: ATM guidance has a significant impact on catheter ablation for PVC. The number of RF applications was reduced. Furthermore, PVC burden at FU was significantly lower in the ATM group, emphasizing its value in RFA of PVC. Moderate success rates may be related to patient selection in a high volume center with a significant number of PVC not originating from the RVOT.

P5335 | BEDSIDE

Decennial analysis of safety in epicardial- and endocardial- vt ablation

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Background: Endocardial- and epicardial- VT Ablations are increasingly performed, but there are still limited information about its safety and complications.
Methods and results: Between 2002 and 2012 complications in 1032 endo- and epicardial- VT Ablations were analysed. In 765 patients (pts; 479 male; 56±15years) 872 endocardial- and in 133 pts (11 male; 52±15 years) 160 epicardial- VT Ablations were performed. Out of 1032 procedures (proc.) in 769 proc. (75%) a retrograde transaortic and in 344 proc. (33%) an antegrade transseptal approach was performed.
A left atrial appendage perforation was observed in 2/344 proc.(0,6%) via the transseptal sheeth, whereas in 1/769 proc. (0,1%) a perforation of the left ventricle (LV) was seen during retrograde transaortic mapping of the LV. A perforation of the right ventricular apex (RVA) during placement of the RV Catheter was presented in 3/1032 proc. (0,3%). Due to epicardial puncture in one patient (0,6%) a perforation of the right coronary artery (RCA) was seen. In two pts (1,3%) a perforation of the liver and in another patient (0,6%) a perforation of the colon was observed. In these three patients the epicardial sheeth was inserted via the liver or colon to the epicardial space. Furthermore in another patient (0,6%) a perforation of the aorta ascendens occured.
Cardiac tamponades/Pericardial effusion were seen in 13/160 proc. (8,1%) during epicardial- and in 10/872 proc. (1,1%) during endocardial-VT Ablation. A none fatal pulmonary embolism occured after epicardial VT Ablation in one patient. A TIA/Stroke could be observed in 2 /872 (0,2%) after endocardial and in 2/160 (1,3%) after epicardial VT Ablation.
Conclusions: The risk of potential severe complications in endocardial- VT Ablation was moderate, whereas in epicardial- VT Ablation a higher incidence was observed.

P5336 | BENCH

Continuous light-induced myocardial alterations and decrease of ventricular fibrillation threshold in hypertensive rats are attenuated by Omacor intake

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Background and purpose: Continuous light suppresses melatonin production that might be deleterious for the heart since melatonin in addition to regulation of circadian rhythms exhibits antihypertensive, free radicals scavenging and antiarrhythmic effects. The latter was recently shown in our study. Deficiency of melatonin as well as omega-3 FA was observed in pts suffering from CHD and hypertension or in hypertensive rats. This can contribute to disease progression and pro-arrhythmia. The purpose of this study was to examine the cardioprotective effects of omega-3 FA intake in hypertensive rats exposed to continuous light.
Design and methods: Male spontaneously hypertensive (SHR) and age-matched normotensive rats were housed under standard 12h light/12h dark cycle or exposed to 24h continuous light/day for 6 weeks. Half of them received Omacor (omega-3 ethyl ester, 25g/kg diet). Left ventricular tissue was used to determine transcription of electrical cell-to-cell coupling protein, connexin-43 (Cx43), pro-inflammatory NFkB and iNOS using real-time PCR. Western blotting was used for protein expression of Cx43 and PKCε. Inducible ventricular fibrillation (VF) was examined using isolated Langendorff-perfused heart.
Key results: Continuous light caused mild elevation of BP in normotensive and enhanced it in SHR as well as decreased threshold to induce VF in both groups comparing to rats under normal light cycle. Myocardial Cx43 mRNA level was not altered, but Cx43 protein and its functional phosphorylated forms (which affect electrical coupling) were decreased in SHR due to continuous light and partially restored by Omacor. Treatment with Omacor also attenuated of continuous light-induced increase of myocardial iNOS and NFkB that are known to down-regulate Cx43. In parallel, the intake of Omacor increased threshold to induce VF.
Conclusions: Findings indicate that continuous light itself affects Cx43 channels-mediated cardiac cell-to-cell communication and enhances propensity of hypertensive rats to malignant arrhythmias. These adverse effects can be, partially, eliminated by treatment with Omacor.
This work was supported by VEGA 2/0046/12, SK-CZ-0027-11 and SKS grants.

P5337 | BEDSIDE
Shape and size of RVOT Isochronal map as a tool to distinguish RVOT/LVOT tachycardia

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In patients with early transition zone (R>S V3) there is a lack of reliable criteria in surface electrocardiographic features for differentiation between right ventricle outflow tract (RVOT) and left ventricle outflow tract (LVOT) premature ventricular contractions (PVCs). This may lead to unnecessary extensive and ineffective energy applications in RVOT in patients (pts) with arrhythmia originating from LVOT Aim of our study was to determine if the data derived from the isochronal mapping such as area and shape of earliest isochron, could improve localization of site of origin (SOO) of outflow tract (OT) PVCs, particularly with V3 transition zone.
Methods: A series of 17 consecutive patients with symptomatic drug refractory PVCs and/or non-sustained or sustained VT originating from the RVOT/LVOT and an apparently normal heart with early transition zone (R>S V3), who underwent successful ablation of OT ventricular arrhythmia was included in the study. Electrophysiological study (EPS) was performed in all patients after written informed consent was obtained. A 6F quadripolar catheter was introduced from the left femoral vein and placed at the right ventricular apex for pacing. Mapping and pacing in the RV were performed using a 7F, 4-mm tip ablation catheter (EZ Steer ThermoCool NAV Bi-Directional, Biosense, Webster). Because the total number of mapped points does not properly reflect the mapping accuracy, the minimum density of points required to include the electroanatomic map of a given chamber was defined as a fill threshold of 10. Electroanatomic 3D mapping data of the right ventricle outflow tract (10-ms isochronal map shape and diameters) were obtained in 9 pts with localization in the LVOT and in 8 pts in the RVOT. The typical 10-ms earliest isochron in RVOT tachycardia was usually round and small (3-6 mm in diameter) comparing to the elliptic form with a shorter longitudinal and longer perpendicular diameter in the case of LVOT site of origin.
Conclusions: In conclusion, in patients with PVCs originating from RVOT, longitudinal/perpendicular ratio of earliest RVOT isochron should be around one. Otherwise LVOT mapping should be considered before any attempt to ablate in RVOT, to avoid unnecessary, ineffective energy applications.

P5338 | BEDSIDE
Steep negative ventricular repolarization restitution slopes are associated with sustained VT/VF in Brugada patients

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Introduction: Brugada patients are exposed to non-sustained and sustained ventricular arrhythmias leading to syncope and/or sudden cardiac death. We aimed to characterize ventricular electrophysiological properties during induced episodes of non-sustained and sustained polymorphic ventricular tachycardia/ventricular fibrillation (pVT/VF).
Methods: In a cohort of 72 Brugada patients, programmed electrical stimulation (PES) induced sustained pVT/VF in 14 patients and non-sustained pVT/VF in 7 patients. Unipolar recordings were used to measure VV interval, maximum conduction velocity (CV) (dV/dt maximum amplitude absolute value), activation recovery interval (ARI) and the slope of ventricular repolarization restitution during pVT/VF was calculated.
Results: As shown in Table, sustained pVT/VF episodes were characterized by shorter VV intervals and steeper restitution slopes. Restitution slopes were negative in 3/7 of non-sustained pVT/VF episodes but in all sustained pVT/VF episodes (p=0.01). Four patients had both sustained and non-sustained episodes. In these 4 patients, restitution slopes were positive (0.24±0.13) during non-sustained episodes but negative during sustained episodes (-0.57±0.41; p=0.01).

Electrophysiological properties	Non-sustained episodes n=7	Sustained episodes n=14	p
VV interval (ms)	194±40	156±12	≤0.01
Maximum conduction velocity (mV/ms)	1.72±1.24	1.00±0.59	0.08
Activation recovery interval (ms)	132±36	111±14	0.07
Repolarization restitution slope	−0.10±0.44	−0.46±0.29	0.04

Conclusion: Ventricular electrophysiological properties are different during sustained and non-sustained ventricular fibrillation in Brugada patients. Steep negative ventricular repolarization restitution slopes are associated with sustained VT/VF in Brugada patients.

P5339 | BEDSIDE
ECG determinants as markers of right ventricular dysfunction in patients with chronic right ventricular volume overload by congenital heart disease

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Pulmonary regurgitation (PR) occurs frequently after surgical correction of tetralogy of Fallot (TF) and congenital pulmonary stenosis (PS). The aim was to determine the power of QRS width (QRSw) to identify RV dilatation and dysfunction. 107 patients with severe PR after TF or PS surgical correction were included. QRSw showed a significant negative correlation with RV ejection fraction and positive correlation with RV volumes (Fig. 1). We determined the optimal cutoff point of QRSw in 140 ms. It showed a good sensitivity for RV dilatation (>80%) and dysfunction (>95%) detection. Logistic regression model identified QRSw>140 ms as the only independent predictor of RV dysfunction and dilatation. QRSw independently predicted RV dysfunction and dilatation.

Baseline characteristics

Age (years)	32±13	QRS width	144.41±28.42
Women n (%)	53 (49.5)	iRVTDV (ml)	145.95±48.03
Tetralogy of Fallot n (%)	80 (74.76)	iRVTSV (ml)	76.04±39.33
Pulmonary stenosis n (%)	27 (25.23)	RVEF (%)	48.93±10.78

iRVTDV, indexed right ventricular end-diastolic volume; iRVTSV, indexed right ventricular end-sysolic volume; RVEF, right ventricular ejection fraction.

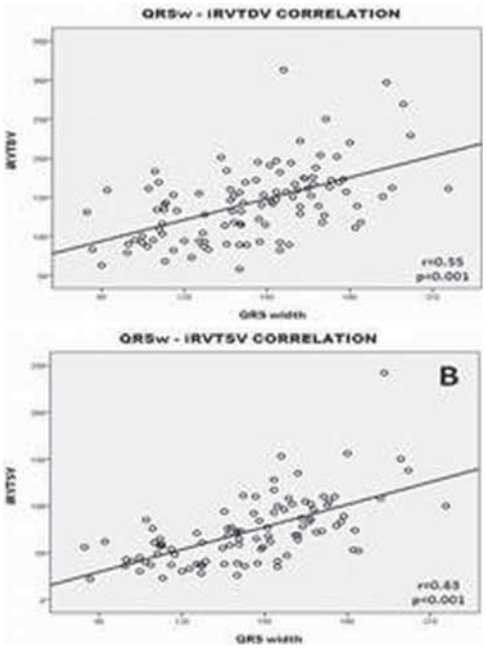

Figure 1

CARDIAC BIOLOGY

P5341 | BENCH
Short-term caloric restriction mediates cardiac redox state and improves diastolic function in pressure overload hypertrophy

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Purpose: Caloric restriction (CR) is known as a powerful intervention to prevent senescent changes, in which reactive oxygen species (ROS) have a critical role. Increasing age is associated with left ventricular (LV) hypertrophy, which is an independent risk factor for the development of cardiovascular diseases. We examined whether CR mediates cardiac redox state and hypertrophy from chronic pressure overload.
Methods and results: Mice were subjected to ascending aortic constriction (AAC) with ad libitum caloric intake (AL+AAC group). In the CR+AAC group, 40% CR was started 2 weeks before aortic constriction. Two weeks after aortic constriction, the ratio of heart weight to body weight significantly increased by 1.6-fold in AL+AAC group. Moreover, AAC increased LV wall thickness and impaired the ratio of the diastolic trans-mitral inflow velocity (E/A), assessed by echocardiography in AL+AAC group. These LV hypertrophy and diastolic dysfunction were significantly attenuated in CR+AAC group. Histological analysis showed that AL+AAC remarkably increased myocyte diameter and interstitial fibrosis, while CR attenuated AAC-induced these morphological changes by 35% and 58%, respectively. Oxidative stress in cardiac tissue was detected by 8-hydroxydeoxyguanosine (8OHdG) expression and mitochondrial oxidative stress was assessed by mitochondrial lipid peroxide level. AAC remarkably enhanced 8OHdG content by 10-fold and mitochondrial lipid peroxide level by 2.2-fold. Furthermore, as major sources of intracellular ROS production, we measured NADPH oxidase activity and mitochondrial ROS production using lucigenin chemiluminescence assay. AAC elevated NADPH oxidase activity by 1.6-fold and mitochondrial ROS production by 1.7-fold in AL+AAC group. CR significantly suppressed these oxidative damages and ROS production. In addition, as intracellular antioxidant systems, we assessed activity of catalase, superoxide dismutase, glutathione reductase (GR), glutathione peroxidase (GPx), and contents of to-

tal glutathione in cardiac tissue. In these antioxidants, myocardial GPx and SOD activities were remarkably enhanced in CR+AAC group compared with AL+AAC group.
Conclusion: Chronic pressure overload significantly increased oxidative stress in cardiac tissue, in associated with cardiac hypertrophy and fibrosis. Short-term caloric restriction mediated cardiac redox state and improved cardiac diastolic dysfunction, suggesting that short-term caloric restriction could be a useful strategy to prevent pressure overload-induced cardiac injury.

P5342 | BENCH
Splenectomy exacerbates pressure overload-induced atrial inflammation and fibrosis in rats

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Purpose: Spleen reserves monocytes, which deploy to inflammatory site to regulate organ inflammation. We aimed to test the hypothesis whether splenectomy (SPX) would promote pressure overload-induced atrial inflammatory fibrosis and atrial fibrillation (AF).
Methods: Six-week old male SD rats were divided into Sham-operation with Sham-operation (Sham+Sham) group, abdominal aortic constriction (AAC) with Sham-operation (AAC+Sham) group and AAC with SPX (AAC+SPX) group. At post operativeday 2, 4 and 28, we performed several examinations.
Results: We observed followings. 1) AAC+SPX for 4 days decreased serum levels of interleukin-10 (IL-10), while increased serum levels of tumor necrosis factor (TNF)-α compared to AAC+Sham ($p<0.01$ and $p<0.05$, respectively). Furthermore AAC+SPX also enhanced the left atrial mRNA levels of TNF-α compared to AAC+Sham ($p<0.05$). In addition, low survival rate is observed in AAC+SPX group at post operativeday 28 compared to AAC+Sham group ($p=0.024$). 2) Western blot analysis revealed that SPX enhanced AAC-induced-overexpression of collagen-1, α-smooth muscle actin, F4/80, monocyte chemoattractant-1 ($P<0.05$, $P<0.05$, $P<0.05$ and $P<0.05$, respectively), while it decreased IL-10 expression ($p<0.01$) at post operativeday 28. 3) At post operativeday 28, left atrium isolated from AAC+Sham group showed inhomogeneous interstitial fibrosis and abundant infiltration of M1 macrophages ($p<0.01$ vs. Sham+Sham group), which were exacerbated by SPX (AAC+SPX group, $p<0.05$). AAC+SPX group also showed diminished recruitment of M2 macrophages in the left atrium compared to AAC+Sham group ($p<0.01$). 4) In isolated-perfused heart experiments, AAC+SPX prolonged interatrial conduction time and AF duration compared to AAC+Sham ($p<0.05$ and $p<0.05$, respectively).
Conclusions: These observations demonstrated that spleen-derived IL-10 plays a remarkable protective role against AAC-induced inflammatory atrial fibrosis and AF. The results also suggest that spleen might be a immunoprotective regulator in response to pressure overload, to prevent cardiac remodeling process via its control of M1/M2 macrophages homeostasis.

P5343 | BENCH
Endonuclease G-like-1 (EXOG), a mitochondrial endo/exonuclease has a role in mitochondrial function and ROS mediated cardiomyocyte hypertrophy

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Purpose: The heart is one of the most energy consuming organs. This energy is used to maintain proper contractile function and is produced mainly in the mitochondria by oxidative phosphorylation (OXPHOS). The production of reactive oxygen species (ROS) is an unavoidable byproduct of OXPHOS. Increased ROS production has detrimental effects on the cells, inducing DNA damage and apoptosis. EndonucleaseG-like-1 (EXOG) and EndonucleaseG are mitochondrial endo/exonucleases with poorly investigated functions in the heart. Whereas EXOG has been implicated in mitochondrial DNA repair, EndonucleaseG appears to play a role in apoptosis, but a recent study in cardiomyocytes showed its importance in mitochondrial function and cardiac hypertrophy. Whether EXOG has additional functions as well, is not clear, but it is interesting to note that EXOG is present in a human genomic locus linked to cardiovascular disease. The goal of this study was to elucidate the role of EXOG in mitochondrial function in cardiomyocytes.
Methods: EXOG adenoviral mediated knock-down was performed in neonatal rat cardiomyocytes. The Seahorse XF24 Extracellular Flux Analyzer was used to measure bio-energetic functions, including OCR (oxygen consumption rate). Mitochondrial parameters including citrate synthesis, mtDNA amount, mtDNA damage and reactive oxygen species (ROS) production were determined. Hypertrophy was assessed by 3H-leucine incorporation and cell surface measurements.
Results: Knock-down of EXOG did not induce mtDNA damage in neonatal cardiomyocytes. Mitochondrial respiration was improved and revealed a 2.4 fold increase in basal mitochondrial OCR ($n=6$, $P<0.05$). Moreover, the ATP-linked OCR was 5.2 fold higher. Western blotting did not showed changes in components of the OXPHOS complex and no changes in mitochondrial biogenesis were observed, suggesting that specific activities in the mitochondria are modulated. Also the membrane potential was not altered, but mitochondrial specific ROS production was strongly increased (5.4 fold) indicating that proper electron transport chain (ETC) flux was impaired. These changes were accompanied by an increase in cellular growth. Interestingly, this hypertrophic response could be attenuated by specific mitochondrial ROS scavengers.
Conclusion: In cardiomyocytes EXOG silencing did not have a direct effect on mitochondrial DNA integrity. However, absence of EXOG increased mitochondrial activity and ROS production, which could be linked to cardiomyocyte hypertrophy.

P5344 | BENCH
Isolation and in vitro characterization of skeletal muscle myoblasts from chronic heart failure patients

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Background: Peripheral muscle wasting is a common finding in CHF. Recent advances in clinical research have confirmed the negative impact of muscle wasting on patient survival. Although innovative research in molecular biology is improving our understanding of how muscle mass is maintained, effective treatment for muscle wasting in CHF has yet to be developed. Consequently, primary skeletal myoblasts cultures from fresh human skeletal muscle biopsies are an attractive tool for investigating skeletal muscle atrophy.
Purpose: To develop a protocol for obtaining pure populations of human chronic heart failure (CHF) myoblasts that can be studied under standardized conditions.
Methods: In vitro myoblasts (n=5 CHF patients) were efficiently isolated and expanded in a controlled environment. Myogenic phenotype and their ability to differentiate into myotubes in vitro was verified by immunostaining and flow cytometry. Cellular viability (Annexine-V) and apoptosis (7-AAD) were assessed using flow cytometry.
Results: Primary muscle cells cultured on single plates revealed a large cell population ($\geq$10 mm) consisting of 90% desmin-positive myoblasts. Immunohistochemistry results showed that desmin and α-actinin proteins were expressed in the cytoplasm of CHF myoblasts. Differentiation of human CHF myoblasts was analyzed until day 6 and myogenesis was characterized by expression pattern of the paired box (Pax) transcription factor Pax7 and by the myogenic regulatory factors (MRFS) myogenic determination factor 1 (MyoD1), Myogenin and MRF4, indicating their skeletal muscle cell identity. Pax7 (72,7% $\pm$ 11,80%) and MyoD1 (82,9% $\pm$ 6,73%) are highly expressed in myoblast cells from CHF patients. CHF myoblast differentiation is marked by the onset of Myogenin expression (13,0% $\pm$ 3,60%) on day 2, whereas levels of MRF4 (72,19% $\pm$ 14,11%) remains stable throughout the process of myogenesis. CHF myoblast cells formed well-developed, multinucleated myotubes. Cell viability ranged from 84,4% to 98,2%.
Conclusion: Overall, satellite cell-derived myoblasts from CHF patients demonstrated a robust proliferation and an excellent differentiation. Skeletal muscle myoblast cell cultures offer the potential for the in vitro study of mechanisms that underlie skeletal muscle wasting in CHF.

P5345 | BENCH
Whole exome sequencing of a family with 3 sibling affected by bicuspid aortic valve disease

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Introduction: Bicuspid aortic valve (BAV) is the most common cardiac malformation affecting 1–2% people worldwide. Despite its high prevalence, the pathogenesis of BAV is largely undetermined, although gene mutations leading to alterations in cell migration and signal transduction, in conjunction with nongenetic factors such as blood flow during valvulogenesis, may contribute to its formation prenatally.
Aim and methods: We applied next generation whole exome sequencing (>3 Gigabases per individual) to identify the genetic factors contributing to BAV presentation in the three daughters and their two unaffected parents. The >36.000.000 sequence reads of each of the 5 individuals was analyzed with the bioinformatical tools Burrows-Wheeler Aligner, SOAPsnp, Samtools, Varscan, and GATK to identify single nucleotide polymorphisms and insertion/deletions.
Results: In each individual we identified over 38,000 SNPs and 3,400 Indels, of which >1,000 and >580, respectively, were novel. Forty one SNPs were detected in at least two of the affected siblings but neither parent, and only 3 of those were detected in all three BAV patients: HFM1 (ATP dependent DNA helicase), TSPAN2 (tetraspanin family member) and TTF2 (transcription termination factor, RNA polymerase II – pre-mRNA splicing regulator). All 3 genes carried exonic, non-synonymous SNVs, with highly significant pathogenicity prediction scores (SIFT, PhyloP, MutationTaster, LRT). Eight Indels were detected in at least two of the siblings, and only one of them was common across all three siblings:

CCNL2 (cyclin L2). CCLN2 is a regulator of the pre-mRNA splicing process, as well as inducer apoptosis by modulating the expression of apoptotic and antiapoptotic proteins. In our patients it was found to carry a four base deletion affecting a splice site.
None of the previously reported BAV-related genes were found to carry a common mutations across all, and unique to the BAV patients of this family.
Conclusion: We have detected 4 genetic variants, shared by all three BAV patients but neither parent. These genes have not been associated with BAV to date. Of particular interest is the novel variant in TSPAN2, a gene of largely unexplored function, belonging to a transmembrane protein family known to mediate signal transduction events that play a role in the regulation of cell development, activation, growth, adhesion and motility.

P5346 | BENCH
Effect of beta-stimulation on failing heart treated with SERCA2a gene transfer

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Purpose: Sarcoplasmic reticulum Ca2+ ATPase (SERCA2a) gene transfer improves calcium regulation and improves cardiac function in heart failure. However, little is known how this treatment influence the response to β-stimulation and the improved function may be achieved at the cost of limited contractile reserve. Our aim was to determine the effects of β-stimulation in the setting of chronic heart failure following SERCA2a gene transfer.
Methods: Twelve pigs developed chronic heart failure 1 month after the induction of an extensive anterior myocardial infarction. Pigs were randomly treated by intracoronary injection of adeno-associated virus 1-SERCA2a (SERCA2a group, n=6) or saline (saline group, n=6). Dobutamine stress test was performed 2 months after the gene transfer with starting doses of 2.5 μg/kg/min followed by stepwise increase up to 20 μg/kg/min. Animals were continuously monitored with electrocardiogram and high fidelity pressure-volume catheter during the Dobutamine infusion. Pressure-volume loop relationship evaluation by preload reduction as well as 3-dimensional echocardiography (3DE) were performed before the infusion and at Dobutamine 2.5 μg/kg/min.
Results: SERCA2a gene transfer improved LV ejection fraction (EF) from before gene transfer to 2 months after without statistical significance (9.5±15.8% vs 0.3±14.3%, P=0.37). However, due to the lower LVEF before the gene transfer in SERCA2a group, there were no differences in all the parameters at the time of Dobutamine test. Low dose Dobutamine (2.5 μg/kg/min) resulted in similar increases in contractility parameters between the groups with LVEF showing tendency towards better improvement in SERCA2a group (%changes before and 2.5 Dobutamine: 3DE-LVEF; 7.5±4.5% vs 1.8±4.9, P=0.06, dP/dt maximum; 127±22% vs 142±67%, P=0.62, Emax: 53±68% vs 20±27%, P=0.30, preload-recruitable stroke work;74±38% vs 64±32, P=0.64, SERCA2a vs saline respectively). At the higher Dobutamine doses, 2 pigs in each group showed sustained ventricular tachycardia which was reversed by stopping the infusion. Highest dP/dt maximum achieved by the Dobutamine infusion was not different between the groups (relative ratio to before Dobutamine; 4.03±0.99 vs 3.88±0.80, P=0.77, SERCA2a vs saline).
Conclusion: SERCA2a gene transfer in chronic heart failure showed similar relative responses to β-stimulation compared to control animals. Moreover, it may result in improved contractile reserve.

P5347 | BENCH
Mutation detection rate and -characteristics in thoracic aortic aneurysm (TAA) related disorders: results from next generation sequencing (NGS) panel testing

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Background: In recent years the genetic basis of Heritable Thoracic Aneurysms and Dissections (H-TAD) has greatly expanded and has enabled gene-tailored management. Attempts to link each gene to a corresponding syndromic entity have failed due to overlapping clinical features and the identification of mutations in non-syndromic patients. This compromises targeted single gene testing and Next Generation Sequencing (NGS) based panel testing of multiple genes has now emerged as a preferred technique. So far, no data on mutation detection rate with this technique have been reported.
Methods: We implemented NGS based screening after targeted PCR enrichment of the 7 most common H-TAD-associated genes (FBN1, TGFBR1/2, SMAD3, TGFβ2, ACTA2 and COL3A1) in the diagnostic workflow. Between November 2012 and December 2013 141 samples from unrelated probands presenting either TAD (N=119), arterial aneurysm/dissection outside the aorta (N=10) or syndromic features with positive family history for TAD (N=12) were sequenced on an Illumina MiSeq sequencer.
Results: The median age of the cohort was 41.7 years (IQR 29.3 – 52.7y). We found a causal mutation in 22 patients (16%)
Clinical and genetic findings are summarized in the table
Conclusion: NGS based gene panel testing in patients with H-TAD efficiently reveals a mutation in 16% of patients. Causal mutations in patients not presenting clinical manifestations of syndromal H-TAD, as well as mutations in genes - other than FBN1 - in patients meeting the diagnostic criteria for specific syndromes including Marfan syndrome are identified, justifying a widespread application of this technique.

Mutations and clinical summary

Gene	FBN1	TGFBR1	TGFBR2	TGFB2	SMAD3	COL3A1	ACTA2
Total	10	1	2	3	2	3	1
Clinic	9MFS	1LDS	1LDS	2S-HTAD	1S-HTAD	1vEDS	1NS-HTAD
	1NS-HTAD		1NS-HTAD	1MFS	1MFS	2NS-HTAD	

MFS, Marfan syndrome; LDS: Loeys-Dietz syndrome; (N)S-HTAD, (non)syndromic HTAD; vEDS, vascular Ehlers Danlos syndrome.

P5348 | BENCH
Endothelial nitric oxide synthase gene polymorphisms and coronary artery disease: Are Asians more vulnerable than other races?

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Purpose: Several positive association studies among Asians for endothelial nitric oxide synthase (eNOS) gene polymorphisms and coronary artery disease (CAD) are recently out in the public domain. However the differential risk of Asians vs. all other races has yet to be ascertained. This prompted us to carry out a meta-analysis separately testing association among studies originating from Asian and Non-Asian ethnicity (NAE).
Methods: We conducted a meta-analysis separately for 28 Asian (11,158 subjects) and 52 NAE (31,492 subjects). We included published case control, association studies with CAD as end point, published up to December 2013, testing common polymorphisms of eNOS gene, namely G894-T (rs1799983), T786-C (rs2070744) and 4b/a (27 bp VNTR of Intron 4). Studies which exclusively covered special populations and with very small sample size (<200 subjects) were excluded to avoid bias. Meta Analyst v2.0® was used to carry out this meta-analysis.
Results: Fourteen studies from Asian (5,496 subjects) and 26 from NAE (16,521 subjects) group were included for G894-T polymorphism. All the genetic models among Asian ethnicity showed significant association (OR's=1.5, 1.9 and 1.4 respectively for dominant, recessive and allelic models, all p=/<0.006). However lower degree of association was seen among NAE and limited to only recessive (OR=1.3, p=0.014) and allelic models (OR=1.1, p=0.036). Four studies from Asian (1,544 subjects) and 12 from NAE (4,862 subjects) group were included for T786-C polymorphism. Among Asians all genetic models showed overwhelming association (OR's=2.0, 2.0 and 1.9 respectively for dominant recessive and allelic models, with all p =/<0.002). This association among NAE was lesser, where only dominant (OR=1.4, p=<0.001) and Allelic models (OR=1.2, p=0.002) showed significant association with CAD. Ten studies from Asian (4,118 subjects) and 14 from NAE (10,109 subjects) group were included for 4b/a polymorphism. The Asians here seem to be lesser associated as only two genetic models yielded significant results (OR=1.2 and 1.3; p=0.04 and 0.002 for dominant and allelic models respectively). On the other hand, NAE showed significant associations for all three models (Similar OR's i.e. 1.3 and p=0.009, 0.008 and 0.001 respectively for dominant, recessive and allelic models)
Conclusions: The present study, which is the most comprehensive meta-analysis till date and creates a better understanding about this gene. It indicates that Asians carrying eNOS G894-T and T786-C polymorphisms are clearly at a higher risk for CAD as compared to that from other ethnicities.

P5349 | BENCH
Mtus1 splice variant inhibits cardiac hypertrophy and exacerbates heart failure

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The molecular mechanisms of heart failure have not been completely elucidated. We performed multiple genome-wide approach using exon array and RNA Sequencing to identify the novel genes responsible for heart failure. We constructed exon and gene expression profiles of murine hypertrophic and failing hearts induced by transverse aortic constriction (TAC) for 8 weeks, and focused on Mtus1 (mitochondrial tumor suppressor 1) gene. Mtus1A, one of the splice variants of Mtus1, was specifically upregulated in failing hearts. The Mtus1A expression level was gradually increased in a time-dependent manner after TAC, and well-correlated with the extent of left ventricular posterior wall thickness (LVPWT). In neonatal rat cardiomyocytes, Mtus1A overexpression decreased phenylephrine-induced MEK and ERK phosphorylation, resulting in a decrease in both cell size and protein synthesis. Furthermore, we observed that TAC-induced increase in LVPWT was suppressed in cardiac-specific Mtus1A transgenic mice (TG) [wild type (WT) vs TG: 0.81±0.03mm vs 0.65±0.02mm; P<0.01]. In addition, LV systolic function was significantly impaired in Mtus1A TG mice after TAC (fractional shortening: 27% vs 11% for WT vs TG, respectively: P<0.01). We conclude that Mtus1A variant inhibits cardiac hypertrophy and exacerbates heart failure through the inhibition of ERK signaling.

P5350 | BENCH

Identification of suitable reference genes for gene expression studies in normal and pathological human heart tissues

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Purpose: Quantitative real-time RT-PCR (RT-qPCR) has become the method of choice for mRNA quantification, but requires an accurate normalization based on the use of reference genes showing invariant expression across various pathological conditions. By contrast, few data exist on appropriate reference genes for human heart. Our aim was to determine a set of suitable reference genes in human atrial and ventricular tissues, from right and left cavities in control and various diseases.
Methods: Expression of 16 reference genes (ACTB, POLR2A, YWHAZ, PGK1, PPIA, GAPDH, IPO8, HMBS, GUSB, 18S, B2M, RPLP0, TBP, TFRP, UBC) was assessed in tissue from right and left ventricle from healthy and heart failure (HF) patients; tissue from right atrium from patients in sinus rhythm (SR) with or without atrium dilatation, patients with paroxysmal atrial fibrillation (AF), with chronic AF or HF; and tissue from left atrium from patients in SR and in AF. RT-qPCR was performed using Taqman® Human Endogenous Control Arrays on a 7900HT system. Expression variability of these genes was evaluated by geNorm and Normfinder algorithms, BestKeeper software tool and comparative Delta-Ct method.
Results: Preliminary consensual analysis of the variability scores obtained for each reference gene expression shows that the most stable genes are: GUSB, IPO8, POLR2A and YWHAZ when comparing either right and left ventricle or ventricle from healthy and HF patients; POLR2A, IPO8, PPIA, HPRT1 and GAPDH when comparing either right and left atrium or atria from all pathological groups. 18S, TBP, ACTB, TFRC and B2M genes were identified as the least stable reference genes, confirming that they are not worth of selection for normalization in human heart samples.
Conclusions: The overall most stable reference genes across different heart cavities and health settings were POLR2A, IPO8, GAPDH, PPIA, YWHAZ and GUSB. RPLP0, PGK1 and HPRT1 could be also a good option for some specific experiments. This study could provide useful guidelines for reference gene selection in qRT-PCR studies in human heart.

CARDIAC ELECTROPHYSIOLOGY: WHEN THINGS GO WRONG

P5352 | BENCH

Sudden death due to left dominant arrhythmogenic cardiomyopathy with digenic heterozygosity: the challenge of risk stratification in familial carriers of single nucleotide variations

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Background: Mutations in genes encoding for desmosomal proteins are the most common cause of arrhythmogenic cardiomyopathy (AC). Compound/digenic heterozygosity has been identified as one of the most important determinants of malignant arrhythmic outcome.
The impact of two single nucleotide variations(SNV) in the AC phenotype expression in a small family was assessed.
Methods: A 40- years old competitive athlete with a history of idiopathic right ventricular outflow tract tachycardia (normal 12 lead ECG and 2D echo) and successful catheter ablation, died suddenly during a cycling competition. Autopsy identified a concealed left dominant AC. Conventional genetic screening for all desmosomal-related AC genes [desmoplakin, desmoglein-2 (DSG2), desmocollin-2 (DSC2), junctional plakoglobin and plakophilin-2, catenin-aT, desmin, phospholamban] and parallel exome sequencing was carried out. SNV segregation and disease penetrance was further assessed in the family members.
Results: By exome and conventional sequencing two SNVs in different desmosomal genes were identified in the proband: one in exon 14 of DSG2, c.2137 G>A (rs79241126, E713K), previously reported in AC cases as an "uncertain" variant with minor allele frequency (MAF) equals to 0.037; and the other SNV in exon 16 of DSC2, c.2603 C>T (rs141873745, S868F), considered a variant "likely to be pathogenic" since can alter the functional properties of the protein, has no available reported MAF and in silico analysis predicted a malignant outcome (Polyphen-2: malignant, SIFT: probably deleterious).
Cascade genetic screening showed that all relatives were carriers for only one of the two SNVs. The father is a DSG2 SNV carrier who holds a pacemaker; the mother is an asymptomatic DSC2 SNV carrier; the brother is a DSC2 SNV carrier and the sister a DSG2 SNV carrier, both exhibiting a less severe AC phenotype with septal and LV late-enhancement at cardiac magnetic resonance, in the absence of ventricular arrhythmias and 2D echo abnormalities.
Conclusions: The data herein reported confirm that digenic heterozygosity predicts a more severe phenotype and arrhythmic outcome in AC. However, the risk conferred by SNV in family members needs to be evaluated further by follow-up studies.

P5353 | BEDSIDE

Genetic screening of sudden cardiac death victims with structural and unspecific abnormalities of the heart

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Purpose: Sudden cardiac death (SCD) is responsible for a large proportion of deaths in young individuals. In a forensic investigation, many of the cases show structural abnormalities, although often unspecific and therefore not diagnostic. A major proportion of these are suspected to be caused by inherited cardiac diseases. It is generally expected that implementation of genetic investigations in forensic medicine may increase the diagnostic rate. The purpose of the study was to explore the yield of genetic testing using next-generation sequencing (NGS) in forensic pathology, by investigating the frequency of pathogenic mutations in a cohort of deceased individuals with structural abnormalities of the heart.
Methods and results: Genetic investigation was performed in unrelated and deceased individuals under the age of 50 with structural abnormalities of the heart. Individuals with a post-mortem diagnosis of hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy or unspecific findings of the heart were included. With Haloplex Target Enrichment System (Agilent), all coding regions of 100 genes associated with inherited cardiomyopathies and channelopathies, were sequenced on the Illumina MiSeq platform. Preliminary results show that 40% of the deceased are identified with a probably pathogenic mutation, likely to be the cause of death.
Conclusions: By investigating a wide range of cardiac associated genes with NGS, it was possible to detect probably pathogenic mutations disposing to a cardiac disease, in suspected SCD victims with structural abnormalities at autopsy. Genetic investigation with NGS can be used as a diagnostic tool in forensic setting.

P5354 | BENCH

Systematic screening of rare coding variants in genes involved in cardiac arrhythmias

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The development of new strategies based on next-generation sequencing enables the large-scale screening of genes involved in rare diseases. We have developed a custom design based on the HaloPlex™ technology to sequence the coding regions of 163 candidate genes, including all genes previously linked to cardiac arrhythmias.
In total, 570 individuals were included in this study. To validate our design, we first analysed 42 patients with inherited cardiac arrhythmias. Among the 69 genetic variants previously identified in these patients, 68 were detected automatically after HaloPlex library preparation and Illumina sequencing. The undetected variant is a substitution located in a low-coverage region. Subsequently, 361 additional patients were analysed (178 patients with Brugada syndrome; 89 patients with early repolarization syndrome; 94 cases of progressive cardiac conduction defects). We also analysed 167 controls, over 65 years of age and showing no signs of cardiac rhythm or conduction abnormalities. The mean coverage was 577X and we found 5 rare functional variants per patient on average. Then, burden tests were performed to detect genes significantly associated to cardiac arrhythmias. This approach also identified potential new disease genes, and replication in an independent cohort is in progress.
Our study will lead to a catalogue of mutations in genes linked to hereditary cases of sudden cardiac death. The systematic screening of our cohorts will also guide our future molecular investigations for these diseases and contribute towards improving the prevention of sudden cardiac death.

P5355 | BENCH

Class I antiarrhythmic drugs target cardiac two-pore-domain K+ (K2P) background channels

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Purpose: Class IC antiarrhythmic drugs are commonly used for rhythm control in atrial fibrillation (AF). In addition, class I drugs are administered to suppress ventricular tachyarrhythmia in selected cases. The multichannel blocking profile

of class I compounds includes reduction of cardiac potassium currents in addition to their primary mechanism of action, sodium channel inhibition. Blockade of two-pore-domain potassium (K2P) channels in the heart causes action potential prolongation and may provide antiarrhythmic action in AF. This study was designed to elucidate inhibitory effects of class I antiarrhythmic drugs on K2P channels.
Methods: Whole-cell patch clamp and two-electrode voltage clamp electrophysiology was used to study K2P channel pharmacology in Chinese hamster ovary cells and Xenopus oocytes.
Results: Human K2P2.1 (TREK-1) and hK2P3.1 (TASK-1) channels were systematically tested for their sensitivity to clinically relevant class IA (ajmaline), IB (mexiletine), and class IC (propafenone) antiarrhythmic compounds. Mexiletine and propafenone inhibited K2P2.1 (IC50 = 182 μM/7.9 μM) and K2P3.1 channels (IC50 = 69.1 μM / 7.5 μM) in mammalian cells. Ajmaline did not significantly affect K+ current amplitudes. K2P channels were blocked in open and closed states, resulting in resting membrane potential depolarization. Open rectification properties of the channels were not affected by class I drugs.
Conclusions: Class I antiarrhythmic drugs target cardiac K2P K+ channels. Blockade of K2P2.1 and K2P3.1 potassium currents is linked to antiarrhythmic therapy and provides mechanistic evidence to establish cardiac K2P channels as antiarrhythmic drug targets.

P5356 | BENCH
Different catecholamines induce different patterns of takotsubo-like cardiac dysfunction in an apparently afterload dependent manner

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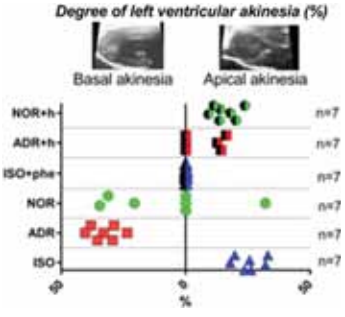
Aims: Takotsubo cardiomyopathy (TCM) is characterized by regional cardiac dysfunction that cannot be explained by an occlusive coronary lesion. Catecholamines are implicated in the pathogenesis but the mechanisms involved are unknown. Because the endogenous and the most commonly used exogenous catecholamines have well defined adrenoceptor subtype affinities, inferences can be made about the importance of each adrenoceptor subtype based on the ability of different catecholamines to induce TCM. We studied which of five well-known catecholamines, with different receptor subtype affinities, that could induce TCM-like cardiac dysfunction in the rat.
Methods: 255 rats received intraperitoneally isoprenaline (β1/β2-adrenoceptor agonist), epinephrine (β1/β2/α-adrenoceptor agonist), norepinephrine (β1/α-adrenoceptor agonist), dopamine (β1/β2/α-adrenoceptor agonist) or phenylephrine (α-adrenoceptor agonist). Each catecholamine was given in five doses. We measured blood pressure through a catheter inserted in the right carotid artery and studied cardiac morphology and function by echocardiography.
Results: All catecholamines induced TCM-like cardiac dysfunction. Isoprenaline induced hypotension and predominantly apical dysfunction whereas the other catecholamines induced hypertension and basal dysfunction. When we continuously infused hydralazine (h) to rats that received epinephrine or norepinephrine to maintain systolic blood pressure <120 mmHg these rats developed akinesia of the apex instead of the base. Infusion of phenylephrine (phe) to maintain blood pressure >120 mmHg after isoprenaline administration prevented apical TCM-like dysfunction.



Conclusions: Catecholamine-induced TCM-like cardiac dysfunction appears afterload dependent rather than dependent on a specific adrenoceptor subtype.

P5357 | BEDSIDE
Exercise training improves arterial baroreflex control of muscle sympathetic nerve activity in patients with chronic heart failure

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Purpose: Previous studies have demonstrated that arterial baroreflex control of muscle sympathetic nerve activity (ABR-MSNA) is impaired in heart failure (HF). We tested the hypothesis that exercise training would improve the oscillatory pattern of muscle sympathetic nerve activity (LF-MSNA/HF-MSNA), and the gain and latency of the ABR-MSNA in patients with chronic HF.
Methods: Twenty-six consecutive, randomized HF patients, functional class II-III NYHA, EF≤40%, peak VO2≤20ml/kg/min were divided into two groups: Trained (T, n=13, 57±2 years) and untrained (UT, n=13, 49±4 years). Muscle sympathetic nerve activity (MSNA) was directly recorded by microneurography and blood pressure was measured on a beat-to-beat basis during 10 min period. Time series of MSNA and systolic arterial pressure were analyzed by autoregressive spectral analysis method. Gain and time delay of the ABR-MSNA was obtained by bivariate autoregressive analysis method. Exercise training was performed on a cycle ergometer at moderate intensity, three 40-min session/week for 16 weeks.
Results: Baseline MSNA, LF-MSNA/HF-MSNA, gain and latency of the ABR-MSNA were similar between T and UT groups. T patients showed decreased resting MSNA (Δ= 15±5 vs. 0±3 bursts/100 heart beats, P=0.02) and increased LF-MSNA/HF-MSNA (Δ= 0.3±0.1 vs. -0.3±0.2, P=0.04) compared to UT patients. In contrast to T patients, UT patients showed a reduction in the gain of ABR-MSNA (Δ= 0.1±0.4 vs. -1.7±0.6, P=0.03) and an increase in the latency of the ABR-MSNA (Δ= 0.4±0.6 vs. 3.3±0.9 s, P=0.02).
Conclusions: Exercise training decreases resting MSNA and improves the oscillatory pattern of MSNA in patients with chronic HF. In addition, exercise training reverses the deterioration in the ABR-MSNA.

P5358 | BENCH
Vagal mechanisms controlling exercise capacity

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Purpose: Remote ischaemic preconditioning known to protect the heart against ischaemia/reperfusion injury increases parasympathetic (vagal) tone and enhances athletic performance. Vagal preganglionic neurones of the dorsal motor nucleus of the vagus nerve (DVMN) mediate remote preconditioning cardioprotection. Since athletes are known to have heightened vagal tone (as measured by heart rate variability and recovery); we used an experimental (animal) model to test the hypothesis that acute withdrawal of vagal tone impairs exercise capacity.
Methods: In male Sprague-Dawley rats (380-420g), a lentiviral vector was used to transduce DVMN neurones to express an inhibitory Gi-protein-coupled Drosophila allatostatin receptor (AlstR) (n=8) or green fluorescent protein (GFP) as a control (n=8). Application of a natural ligand of AlstR - an insect peptide allatostatin (5 μl) produces selective and rapid silencing of targeted neurones. A separate pharmacological study investigated the role of muscarinic and neuronal nitric oxide-mediated mechansims using systemic treatment with atropine methyl nitrate (2mg/kg, i.p., n=5) or selective neuronal NO synthase inhibitor 7-nitroindazole (7-NI) (30mg/kg, i.p., n=8).
Forced exercise experiments were conducted on a single rodent lane treadmill with a shock grid set at the minimum threshold of 0.1 mA. Rats were preselected for their compliance after a three day recruitment protocol and randomly allocated. The recruitment protocol involved speeds of 20-30 cm/s over 5 minutes after 15 minutes of acclimatisation. Speeds were then raised in increments of 5 cm/s in 5 minute intervals until the hind limbs made grid contact four times within a two minute period. The calculated work done (Joules, J) was used as an index of exercise capacity.
Results: Baseline exercise capacity was similar in rats expressing AlstR and GFP in the DVMN (46.2±4.6J vs 58.8±7.2J, p=0.4304). Acute inhibition of the DVMN vagal preganglionic neurones following allatostatin application resulted in a dramatic reduction in exercise capacity (8.1±2.2J vs 62.1±8.7J, P<0.0001). In rats given atropine methyl nitrate and vehicle no significant difference in exercise capacity was noted (112.8±20.4J vs 111.7±22.4J, p=0.8652). 7-NI however, produced a significant reduction compared to vehicle (32.63±19.2J vs 128.9±19.2J, p=0.0002) as did 4 hours of methyl atropine (63.1±12.3J vs 116.2±19.7J, p=0.0019).
Conclusion: Results of these experiments suggest that parasympathetic tone generated by the DVMN neurones controls exercise performance via a NO-mediated mechanism.

P5359 | BENCH
Intravenous vagal nerve stimulation (VNS) in acute myocardial infarction (AMI) markedly reduces the infarction size and improves cardiac function in the chronic phase

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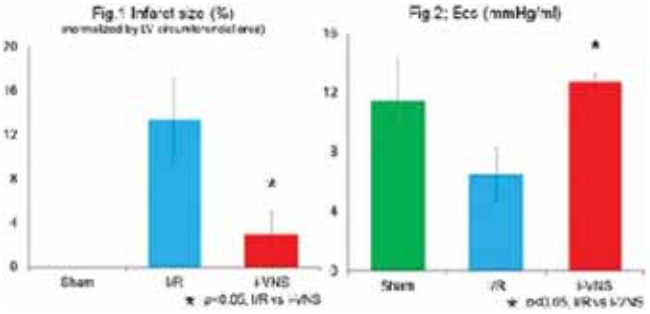
Purpose: Despite the widespread practice of coronary reperfusion therapy, AMI remains one of the major causes leading to heart failure in the long term. Although

VNS has been shown to exert powerful anti-infarct effects, the technical difficulty associated with VNS precludes its application under emergent settings of AMI. In this study, we developed a novel technique of intravenous VNS and evaluated how the VNS affects the infarct size and cardiac function 4 weeks after AMI with reperfusion.
Method: In 11 mongrel dogs, we ligated a left anterior descending coronary artery for 3 hours, then reperfused. For the intravenous VNS, we performed the field electrical stimulation between a pacing catheter in the superior vena cava and an electrode pad attached to the back. We delivered VNS from the beginning of ischemia to 1 hour after reperfusion. We titrated the strength of VNS to lower heart rate by 20–30%. We divided animals into 3 groups, sham operation/no stimulation (Sham, N=3), ischemia-reperfusion (I/R, N=4), and I/R+VNS (I/R-VNS, N=4). 4 weeks after ischemia, we evaluated hemodynamics and left ventricular function in terms of end-systolic elastance (Ees). We also histologically estimated the infarct size.
Results: During operation, mean heart rate were significantly lower in I/R-VNS than in I/R (107±20 vs. 134±16 bpm, $p<0.05$), while blood pressure didn't differ among 3 groups. I/R-VNS strikingly decreased the infarct size more than 80% ($p<0.05$, Fig. 1) and improved Ees ($p<0.05$, Fig. 2). I/R-VNS markedly decreased left ventricular end-diastolic pressure (5.0±1.6 vs. 23.8±2.5 mmHg, $p<0.05$) and serum NT-pro BNP (843±256 vs. 3667±1637 pmol/ml, $p<0.05$).



The effect of VNS for infarct size & Ees.

Conclusion: Intravenous VNS in AMI markedly reduces the infarct size and improves cardiac function in the chronic phase.

P5360 | BENCH
Funny current mediated pacemaker activity in the sinoatrial node of sodium-calcium exchanger knockout mice

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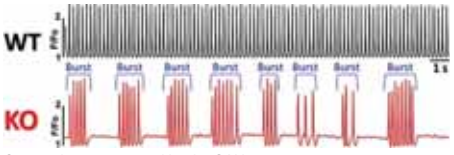
Purpose: The sodium-calcium exchanger (NCX) is the major Ca extruder of myocytes. In the sinoatrial node (SAN) both NCX and funny current (If) participate in the depolarization that initiates pacemaker activity. To clarify the relative contribution of NCX to SAN pacing, we created an atrial-specific NCX knockout (KO) mouse. This mouse does not express any NCX in the atrial region, including the SAN. Phenotypically, NCX KO mice lack P waves on their electrocardiograms and have quiescent isolated SAN cells. Recording the Ca dynamics in a novel preparation that includes the SAN and atria, we investigated wether atrial remodelling may have obscured residual pacemaker activity in NCX KO SAN tissue.
Methods and results: Using high speed 2D confocal microscopy we found that the KO SAN exhibited bursts of organized Ca transients alternating with pauses, characterized by abundant intracellular Ca waves. Although, the overall rate of Ca transients in NCX KO SAN (~2Hz; n=25) was reduced by the numerouse pauses, the frequency of Ca transients during the bursts was rapid. Their average frequency (~4Hz; n=24) was not significantly different from WT (~5Hz; n=24). When considering only the rate during the burst, we found that 6 out of 10 KO SANs responded significantly to β-adrenergic stimulation (isoproterenol 10μM; 52±16% rate increase). This response was smaller but still comparable to the increase in WT SANs (70±6%; n=5). The pacemaker activity of both genotypes responded to the If blocker ivabradine (IVA, 9μM). At higher doses of IVA (27μM) WT SANs decreased their rate by 43±4%, while KO SAN Ca transients were effectively eliminated.



Ca transients generated by the SAN.

Conclusions: These results indicate that If generates the burst pacemaker activity found in the NCX KO SAN, and allows the partial β-adrenergic responsiveness of the KO.

P5361 | BENCH
Pitx2 decreases L-type Ca2+ current and increases the slow delayed rectifier K+ current in cardiac cells

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Purpose: Genome wide scan analyses demonstrated that single nucleotide polymorphisms in the human chromosome 4q25, proposed to regulate the activity of the adjacent transcription factor Pitx2, were associated with an increased risk in atrial fibrillation (AF). Recent evidence has shown that Pitx2 could play a role in AF-induced electrical remodelling. However, its putative role in the control of expression/function of the ion channels responsible for atrial action potential is currently unknown. This work was undertaken to determine the effects of Pitx2 on voltage-gated cardiac Ca2+ and K+ channels.
Methods: Currents were recorded in HL-1 cells transfected or not with the cardiac Pitx2 isoform (Pitx2c) by using whole-cell patch-clamp. L-type calcium current (ICa,L) was recorded by using Ba2+ as charge carrier (IBa).
Results: Under control conditions, peak IBa density was reached at +20 mV (-4.6±0.6 pA/pF). Pitx2c significantly reduced peak IBa density (-2.8±0.3 pA/pF at +20 mV, $P<0.05$) without modifying activation, inactivation, and reactivation kinetics or voltage- dependent activation and inactivation. Regarding voltage-gated K+ channels, under control conditions 2 groups of cells were identified based on the predominant voltage-gated K+ current exhibited. In most of the cells (≈80%), a rapid delayed rectifier current (IKr) sensitive to dofetilide could be recorded, which reached a mean density of 1.9±0.2 pA/pF at 0 mV. In the rest of the cells (≈20%), IKr was absent and the predominant current was a fast activating and slow inactivating outward current sensitive to 4-aminopyridine (2 mM), with biophysical properties compatible with the ultrarapid delayed rectifier K+ current (IKur) recorded in human atrial myocytes. In the presence of Pitx2c, only a small subset of the cells exhibited IKur (≈10%) sensitive to 4-aminopyridine. Importantly, most of the cells (≈90%) exhibited a voltage-gated, dofetilide-resistant, K+ current with a very slow activation kinetics (τact at +60 mV= 1.8±0.3 s) that reached 8.9±3.0 pA/pF after 5-s pulses to +60 mV. The mean midpoint of the activation curve was 20.0±3.9 mV. This current was completely abolished by HMR-1556 (1 μM). All the biophysical and pharmacological properties of the Pitx2c-induced current resembled those of the human cardiac IKs.
Conclusions: The results demonstrated that Pitx2c decreased ICa,L and increased IKs and suggested that this transcription factor could contribute to the reduction of ICa,L and the increase of IKs that characterise the AF-induced electrical remodelling.

CARDIAC HYPERTROPHY AND HEART FAILURE

P5363 | BENCH
CTCF is prerequisite for the fetal gene expression in the process of hypertrophy of the cardiomyocyte

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Purpose: CCCTC-binding factor (CTCF) is a multifunctional chromatin modulator protein in the nucleus and regulates the phenotypic changes in differentiation or carcinogenesis in various types of cells. We hypothesized that CTCF is one of the master weaver of the cardiac genome and first investigated its roles in the fetal gene expression on the process of cardiac hypertrophy.
Methods: Neonatal rat cardiomyocytes (2-3 do) were cultured. CTCF mRNA was either knocked-down using siRNA or over-expressed by transfection with plasmid loading full-length CTCF cDNA. Hypertrophic stimulation were given by angiotensin II (AII: 0.1-0.4μM) or norepinephrine (NE: 1μM) for 24hrs. Gene expression was investigated by real-time PCR analysis using SYBR-Green method. Microarray profiling analysis of mRNAs was performed.
Results: Immunofluorescence and western blot showed CTCF localized in the nuclei of the cardiomyocytes. Knocking down of CTCF mRNA (-61±4%,n=4) suppressed the gene expression of both β-myosin heavy chain (β-MHC) (-45±7%, $p<0.01$) and α-skeletal actin (α-SA) (-25±3%, $p<0.01$). Pre-treatment with 5-Aza-2'-deoxycytidine (2μM) cancelled these suppressive effects by knocking down of CTCF (n=3), indicating DNA methylation is involved in the function of CTCF. After stimulation with AII or NE cell surface area was significantly increased, indicating hypertrophy occured. Under knocking down of CTCF (n=8), up-regulation of β-MHC mRNA to 190±17% following stimulation with AII (n=4) was suppressed to 123±21% ($p<0.01$), and up-regulation of α-SA to 191±22% was also suppressed to 108±9% ($p<0.01$). With NE (n=4) up-regulation of β-MHC to 155±24% was suppressed to 51±7% ($p<0.01$), and up-regulation of α-SA to 159±23% was also suppressed to 42±5% ($p<0.01$). On the other hand, only over-expression of CTCF (n=4) increased the gene expression of β-MHC to 204±18% andα-SA to 134±17% ($p<0.01$). But, unexpectedly it suppressed the up-regulation of β-MHC to 110±12% and α-SA to 106±11% following stimulation with AII ($p<0.01$,n=4). The extent of α-MHC mRNA was not significantly changed after gain or loss of CTCF. Microarray profiling analysis after knocking down of CTCF demonstrated significant down-regulation of 56 genes including WNT1 inducible signaling pathway protein 2, and significant up-regulation of 50 genes including G-protein coupled receptor 37.

Conclusions: Appropriate amount of CTCF is necessary for the fetal gene expression program in cardiac hypertrophy. CTCF has the possibility to link functionally with the signal transduction pathways from the cell surface.

P5364 | BENCH
GRK2 - PI3K interaction regulates cardiac hypertrophy

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Purpose: The increase in protein activity and upregulation of G-protein coupled receptor kinase 2 (GRK2) is a hallmark of cardiac stress and heart failure. Inhibition of GRK2 has shown to improve cardiac function and survival and moreover diminished cardiac remodeling in various animal models of cardiac disease suggesting potential involvement in cardiac hypertrophy. We have previously shown that conditional GRK2-KO mice present attenuated hypertrophic response with maintained ventricular geometry and heart-to-body weight ratio following aortic constriction while wildtype mice present hypertrophy and dilatation. Hence the aim of the present study was to further enlighten the molecular effects of GRK2 on cardiomyocyte hypertrophy.
Methods: We investigated neonatal rat ventricular cardiomyocyte (NRVCM) under stimulation with different G-protein-coupled receptor agonists. The impairment of GRK2 was investigated using siRNA against GRK2. Cell area, fetal gene expression and total protein extracts were analyzed including phospho-blots of the corresponding signaling pathways. Nuclear NFAT accumulation was investigated by NFAT-promoter luciferase assay. GRK2 binding with possible interaction partners was verified using an immuno proximity ligation assay.
Results: Isolated neonatal rat ventricular cardiomyocytes showed significant upregulation of GRK2 mRNA and protein levels following phenylephrine (PE) and angiotensin II (ANG II) stimulation with resulting hypertrophy. These findings were reproducible by adenoviral GRK2 overexpression. The increase in cell size as well as the observed upregulation of fetal gene response could be abolished by siRNA mediated GRK2 knockdown.
Increased NFAT activity and increased glycogen synthase kinase-β (GSK3β) phosphorylation under adenoviral GRK2 overexpression suggested the PI3K/Akt pathway as the critical signaling cascade of the observed hypertrophic response. This could be affirmed by increased Akt/PKB phosphorylation in both PE and ANG II stimulated myocytes as well as GRK2 overexpressing cardiomyocytes.
Interestingly pharmacological inhibition of PI3K by Wortmannin abolished the hypertrophic effect of GRK2 overexpression, resulting in decrease of Akt phosphorylation, activation of GSK3β and consequently decreased NFAT activity with abolishment of cardiomyocyte hypertrophy.
Conclusion: Our data show a novel role of GRK2 promoting cardiac hypertrophy by GRK2-PI3K mediated Akt phosphorylation and inactivation of GSK3β resulting in enhanced NFAT activity. Thus GRK2 knockdown could be a promising therapeutic approach targeting cardiac hypertrophy.

P5365 | BENCH
Pressure overload to the heart induces pulmonary up-regulation of genes coding secretory proteins involved in the cardiovascular diseases

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Purpose: Recent studies have revealed the importance of the cross-talk between the heart and other organs in the pathophysiology of heart failure (HF). The peripheral blood pressure of the pulmonary circulation is constantly affected by the hemodynamic properties of HF, while secretory proteins from the lung directly reach cardiac tissues through the coronary artery. However, the cardiopulmonary interaction in HF has not been fully elucidated. To investigate how the lung contributes to the pathophysiology of HF, we conducted comprehensive gene expression analysis using DNA microarray.
Methods: We induced heart failure in mice by transverse aorta constriction (TAC, n=3) and created shams (n=3). Eight weeks after operation, echocardiogram was performed and the RNA samples extracted from the lungs were analyzed using Affymetrix GeneChip mouse genome 430 2.0 array. The obtained data were analyzed with GeneSpring Gx version 12.5 and Ingenuity Pathway Analysis.
Results: The TAC-mice showed significantly larger lung weight-body weight ratio and smaller %fractional shortening compared to shams (10.7±3.3 vs. 6.8±1.7, 14±7.0 vs. 32±4.8, $p<0.05$, respectively). Of 45101 probe sets on the microarray, we excluded 23552 probe sets without any expression in all samples and finally investigated 21549 probe sets. Then we focused on 451 probe sets which showed more than 1.5 fold up-regulation in the lungs of TAC-mice compared to shams ($p<0.05$). Among them, 44 were indicated as secretory proteins while 407 were non-secretory proteins. Interestingly, representative functions of up-regulated secretory proteins were related to cardiovascular disease, cellular growth and proliferation, cellular development and cardiovascular system development and function, whereas up-regulated non-secretory proteins were to endocrine system disorders, cell morphology and hematological system development and function. The up-regulated genes coding secretory proteins included growth factors, namely PGF, GDNF, TGFβ1, VEGFC and HB-EGF, as well as proteins involved in Wnt signaling, namely WNT7A, WISP1 and C1q, which activates canonical Wnt signaling in the heart.
Conclusions: The HF induced by pressure-overload to the heart affect the global gene expression of the lung including up-regulation of genes coding secretory proteins involved in cardiovascular diseases and cardiac functions. The reactive pulmonary expression of secretory proteins may play pivotal role in the cardiopulmonary interaction and contribute to the pathophysiology of the HF.

P5366 | BENCH
HDAC inhibition by Entinostat exerts complex effects on electrophysiology, cardiac structure and gene expression profile in pacing induced heart failure in vitro and in vivo

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Background: Tachyarrhythmias exert complex effects on cardiomyocytes and cardiac fibroblasts. Epigenetic changes such as histone acetylation patterns in response to tachyarrhythmias are not well characterized. Histone deacetylase (HDAC) inhibitors hold great promise for the therapy of several malignant diseases, however, little is known about their cardiac effects. Here, we describe the effects of cardiac pacing in combination with Entinostat on cultured cardiomyocytes in cell culture and in an in vivo model of pacing induced heart failure.
Methods and results: Cultured cardiomyocytes were electrically stimulated using a field stimulator. Rabbits were implanted a pacemaker system, subjected to rapid ventricular pacing and treated subcutaneously with Entinostat or carrier, respectively. Following a stimulation period of 10 days, rabbit hearts were explanted, perfused in a Langendorff apparatus and electrically stimulated to determine electrophysiological key parameters. In vitro, Entinostat treatment led to an elevated level of histone 3 acetylation. p21, a known HDAC target gene, was upregulated in response to Entinostat treatment and pacing alone, while combined pacing and Entinostat treatment downregulated p21. Moreover, microarray analysis of mRNA derived from paced cultured cardiomyocytes revealed that electrical stimulation induced cell stress and DNA damage responses. Stimulated cells displayed an enrichment in key genes involved in mediating DNA damage responses and apoptosis, including p21 and Casp, and in components of the ERK/MAPK signaling pathway, a well-known cellular stress response cascade. Simultaneous Entinostat treatment effectively counteracted several of these adverse effects. In vivo, rapid ventricular pacing caused an elevation of monophasic action potential (MAP) duration compared to sham hearts under proarrhythmogenic conditions, while treatment with Entinostat could partially abolish this effect. Finally, the growth of cardiac fibroblasts could be effectively suppressed by Entinostat in vitro. Correspondingly, histological analysis of tissue specimen of rabbit hearts revealed that Entinostat could prevent the development of cardiac fibrosis in response to rapid ventricular stimulation.
Conclusion: HDAC inhibition by Entinostat exerts complex effects on paced cardiomyocytes and can protect cardiomyocytes from electrical remodelling. In addition, Entinostat effectively suppressed fibroblast proliferation in vitro and cardiac fibrosis in vivo. In summary, Entinostat might be a promising candidate for the pharmaceutical therapy directed against cardiac remodelling.

P5367 | BENCH
SIRT3 deficiency impairs mitochondrial and contractile function in the heart

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Rationale: Impairment in mitochondrial energetics is a hallmark of various cardiac pathologies, including the diabetic or the failing heart, but the underlying mechanisms remain incompletely understood. The mitochondrial NAD+-dependent deacetylase sirtuin 3 (SIRT3) regulates enzyme activity by reversible protein lysine acetylation, including enzymes involved in mitochondrial energetics.
Objective: To investigate the role of Sirt3 in the regulation of myocardial energetics and function.
Methods and results: SIRT3–/– mice develop progressive age-related deterioration of cardiac function, as evidenced by a decrease in ejection fraction (-10%) and an increase in enddiastolic volume (+26%) at 24 but not 8 weeks of age using echocardiography. Four weeks following transverse aortic constriction, ejection fraction was further decreased in SIRT3–/– mice compared to WT

mice (-31% vs. -25%), accompanied by a stronger degree of cardiac hypertrophy (heart weight-tibia length ratio 9,3 vs. 13,1; all $p<0.05$). In isolated working hearts, a decrease in cardiac power (-28%) was accompanied by a decrease in palmitate oxidation (-33%), glucose oxidation (-39%), and oxygen consumption (-17%), whereas rates of glycolysis were increased (+40%; all $p<0.05$). Respiratory capacity (-36%), ATP synthesis (-55%) and the ATP/O ratio (-33%) were decreased in cardiac mitochondria from SIRT3–/– mice. HPLC measurements revealed a decrease of the myocardial ATP/AMP ratio (-21%) and of myocardial energy charge (-8%). Using LC-MS/MS, we identified increased acetylation of 85 mitochondrial proteins, including 6 enzymes of fatty acid import and oxidation, 50 subunits of the electron transport chain, and 3 enzymes of the tricarboxylic acid cycle.
Conclusions: SIRT3 is required to maintain mitochondrial and contractile function in the heart, and may regulate myocardial mitochondrial energetics by reversible acetylation of various energy metabolic enzymes.

P5368 | BENCH
Oestradiol improves mitochondrial function and prevents cardiac diastolic dysfunction in a mouse model of human hypertrophic cardiomyopathy mutation

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Purpose: Clinical findings show that female sex and/or the sex hormone estrogen (17β-estradiol, E2) may contribute to the sexual dimorphism in hypertrophic cardiomyopathy (HCM). However, the underlying mechanism is not completely known. Taking into account the sexual dimorphism in cardiac metabolism and function, the aim of the project was to explore the effect of ovariectomy (OVX) and 17β-estradiol (E2) replacement on myocardial and mitochondrial functions in cTnT-Q92 transgenic mice, generated by cardiac-restricted expression of human HCM mutation.
Methods: The cTnT-Q92 mice were ovariectomized at twenty weeks of age and were treated with placebo (OVX group) or E2 (OVX+E2 group) for twelve weeks before sacrifice. Wild-type and cTnT-Q92 female mice with sham operation were used as control groups. Echocardiographic recording and histopathological studies were performed. At the mitochondrial level, respiratory control and ATP levels were determined. Some key components related to mitochondrial energy metabolism such as peroxisome proliferator-activated receptor (PPAR) α, PPARγ coactivator 1α (PGC-1α) and their downstream molecules were also performed using western blot and RT-PCR analysis. The levels of oxidative damage markers and antioxidant defence were determined.
Results: cTnT-Q92 mice had impaired diastolic compared with wild-type mice. In response to ovariectomy, cardiac diastolic function further decreased. Myocardial energy metabolism such as ATP levels and mitochondrial respiratory ratio also decreased significantly in OVX group. Consistent with this, PGC-1α and PPARα also decreased significantly. E2 supplementation partially restored the mitochondrial function as well as reduced oxidative damage, thus improved diastolic function.
Conclusion: Our study showed that administration of 17β-estradiol improved myocardial diastolic function, prevented myocardial energy disorder as well as reduce myocardial oxidative stress in R92Q mice. The significance of the findings is further enhanced in view of E2 on phenotype modification role in HCM.

P5369 | BENCH
PGC-1 alpha pathway regulates cardiac metabolic changes in porcine model of ST segment myocardial infarction

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Purpose: In the context of myocardial infarction (MI) the availability of metabolites is clearly restricted, therefore a fuel metabolic shifts takes place. Previous studies have indicated that peroxisome proliferator activated receptor co-activator alpha (PGC-1α) pathway is a crucial regulator of cardiac metabolism in response to cardiac stress. Here we address the role of PGC-1α in regulating metabolic changes of MI.
Methods: We studied a group of 12 common swine in which anterior MI was induced by means of angioplasty balloon inflation. A series of 6 swine were sacrificed at 48h post-infarction (acute infarction group) and another series of 6 swine were sacrificed at 3 weeks (chronic infarction group). Metabolites such as: glucose, pyruvate, ketone bodies, and lipids were analyzed in serum (mmol/L) at baseline, 75 min after balloon inflation, 2 h, 48 h and 3 weeks after reperfusion by means of enzymatic analysis. Results were compared to baseline levels. Genes related to PGC-1α such as: PGC-1α, ERR-α, PPAR-α, and HIF-1α, were analysed (fold change) in infarcted, adjacent and remote areas of porcine hearts 48h or 3 weeks post-infarction by molecular biology. Results were compared to 5 control swine without infarction.
Results: In all groups, after 2h of infarction, a striking increase of lactate (3.2±0.6 vs. 0.8±0.3) and non-esterified fatty acids (0.6±0.2 vs. 1.8±0.3) was observed in serum compared to baseline ($p<0.001$ in both cases). Conversely, a significant decrease of glucose (5.2±0.3 vs. 3.8±0.2) and β-Hydroxybutyrate (1.8±0.5 vs. 0.6±0.2) occurred at the same time ($p<0.001$ in both cases). All values reverted progressively to baseline after 3 weeks. In comparison with controls, molecular biology analysis of acute infarcted hearts revealed a significant decrease of expression in mRNA and protein levels of transcription factors related to lipid and mitochondrial metabolism: PGC-1α(0.3±0.1 vs. 1.2±0.2 fold), ERR-α(0.8±0.3 vs. 1.6±0.2 fold) and PPAR-α(0.9±0.3 vs. 1.7±0.2 fold) ($p<0.01$ in all cases). Values didn't change after 3 weeks. However genes related to glucose metabolism were significantly increased in acute infarcts compared to controls: GLUT-1 (3.8±0.4 vs. 1.1±0.3 fold), HIF-1α(4.2±1.3 vs. 1.0±0.2 fold) ($p<0.01$ in both cases). These values recovered control levels after 3 weeks.
Conclusion: A metabolic deregulation mediated by PGC-1α decreased expression takes place in the context of acute MI. This is mediated by a decrease of fatty acid oxidation and an increase of glucose utilization and it reverts after 3 weeks.

P5370 | BENCH
SIRT3 deficiency exacerbates LPS-induced cardiac dysfunction

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Myocardial dysfunction is a well described complication of endotoxemia and sepsis, which may be related to simultaneous development of myocardial mitochondrial dysfunction. The mitochondrial NAD+-dependent deacetylase Sirtuin 3 (SIRT3) improves mitochondrial function and decreases mitochondrial ROS production. Since sepsis results in cardiac NAD+ depletion, we hypothesized that impairment in SIRT3 activity due to NAD+ depletion may contribute to the development of myocardial mitochondrial and contractile dysfunction under septic conditions. SIRT3–/– or wildtype mice were investigated 6 hours following injection of E. coli lipopolysaccharide (10 mg/kg) or saline. In isolated working hearts, wild type animals treated with LPS showed a decrease in aortic developed pressure (15.0±0.4 vs. 17.4±0,5 mmHg; $p<0.05$), cardiac power (25.1±1 vs. 31.8±1 mW/g; $p<0.05$), palmitate oxidation (494±28 vs. 335±15 nmol/min/g; $p<0.05$) and cardiac efficiency (4.0±0.3 vs. 6.0±0.4%; $p<0.05$) without changes in myocardial O2 consumption (MVO2). Additional deficiency of SIRT3 resulted in further impairment of contractile parameters, accompanied by a marked decrease in cardiac efficiency (-51%, $p<0.001$) and an increase in MVO2 (+22%, $p<0.05$) when animals were treated with LPS. This decrease in cardiac efficiency was accompanied by unchanged mitochondrial ADP-stimulated O2 consumption in isolated mitochondria, whereas ATP synthesis was reduced, suggesting mitochondrial uncoupling. Thus, acute endotoxemia impairs cardiac contractility, and additional SIRT3 deficiency further impairs cardiac dysfunction and impairs cardiac efficiency, possibly due to increased mitochondrial uncoupling. Impaired SIRT3 activity due to preexisting myocardial NAD+ depletion, as may occur in many cardiac pathologies, may predispose the heart for exacerbation of cardiac dysfunction under septic conditions.

P5371 | BENCH
Different characteristics of diabetic cardiomyopathy in rat models of type-1 and type-2 diabetes mellitus

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Purpose: Diabetic cardiomyopathy, a cardiac manifestation of diabetes mellitus (DM), is characterised by specific structural, molecular and functional alterations of the myocardium. Upon this concept we investigated whether type-1 or type-2 diabetes lead to different alterations in cardiac function or histological and molecular changes.
Methods: Our experiments were carried out in a rat model of type-1 (streptozotocin induced) and type-2 DM (Zucker Diabetic Fatty rats). Left ventricular (LV) function was characterised using a pressure-volume (P-V) conductance catheter system. Load independent indices of LV contractility (preload recruitable stroke work (PRSW)) and indices of LV relaxation (time constant of LV pressure decay (Tau)) and stiffness (LV end-diastolic pressure (LVEDP)) were calculated, respectively. In addition to our functional measurements TUNEL assay was performed to evaluate degree of apoptosis. Myocardial gene expression analysis was performed by qRT-PCR, expression of proteins was investigated by western blot and immunohistochemistry.
Results: In comparison to the control, type-1 DM resulted in decreased LV systolic performance: decreased systolic pressure, maximal dP/dt and PRSW (45.39±2.45 vs 76.44±4.06 mmHg). Type-2 DM was associated with increased LV stiffness (LVEDP: 9.4±0.5 vs 7.7±0.4 mmHg) while systolic indices were altered only to a lower extent. We observed cardiac hypertrophy and degeneration with histomorphological examination. More pronounced nitro-oxidative stress resulted in more severe DNA-damage. Overexpression of c-fos and c-jun and downregulation of eNOS were observed in type-1 diabetic rats. On the other hand TGF-β1 and ANF mRNA-levels were significantly higher in type-2 diabetic model.
Conclusions: Diabetic cardiac alterations are characterised by decreased systolic performance and impaired relaxation in type-1 diabetic rats, while diastolic dysfunction was more pronounced in type-2 DM. In the background of diabetic cardiomyopathy different processes can be identified in the two models. (Supported by the grant OTKA PD100245)

P5372 | BENCH

The GLP-1 metabolite (9-37) improves myocardial function in the TAC model by reducing myocardial hypertrophy and improving glucose uptake

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Introduction: Diastolic dysfunction and myocardial hypertrophy are early signs of hypertensive cardiomyopathy. GLP-1 (7-37) is an incretin hormone which is released in response to nutritional stimuli from the gut and improves glucose metabolism by increasing glucose dependent insulin secretion from the pancreas. GLP-1 (7-37) is rapidly cleaved to its inactive metabolite GLP-1 (9-37) which is unable to bind to the GLP-1 receptor and does not cause insulin secretion. Nevertheless both peptides have been found to hold cardioprotective actions.
Methods and results: To investigate the effects of GLP-1 on hypertensive cardiomyopathy we injected 6 week old C57BL/6J mice with an adeno associated viral vector system overexpressing GLP-1 (7-37), GLP-1 (9-37) or Lac Z (control) (n=15/group). Cardiac hypertrophy was induced by transversal aortic constriction (TAC). Overexpression of GLP-1 (7-37) led to the expected improvement of glucose metabolism ($p<0.01$) while GLP-1 (9-37) had no effect. Despite, both peptides similarly reduced myocardial hypertrophy ($p<0.01$; n=5-10/group) and reduced myocardial collagen content (gomori stain and PCR all $p<0.05$; n=6-8/group) and apoptosis (caspase-3 $p<0.05$). Interestingly however, only GLP-1 (9-37) led to a significant improvement of diastolic myocardial function (dp/dt-min) while reducing LVEDP (all $p<0.05$; n=13/group after 4 weeks under dobutaminstress by millar catheter). This was accompanied by a significant reduction of myocardial F18-FDG-glucose uptake ($p<0.05$; n=11/group in the PET) in GLP-1 (9-37) expressing mice and reduced expression of the glucose transporters GLUT1 ($p<0.01$) and GLUT4 ($p<0.01$). In addition, GLP-1 (9-37) expressing mice were found to hold increased ACC phosphrylation ($p<0.05$) pointing to activation of AMPK as a possible mechanism.
Conclusion: The GLP-1 metabolite (9-37) improves hypertrophic cardiomyopathy in the TAC model by reducing myocardial glucose uptake, ventricular hypertrophy

IMAGING AND CARDIAC MECHANICS

P5374 | BEDSIDE

Left ventricular rotational mechanics in cirrhotic patients: a speckle-tracking echocardiographic study

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Purpose: Cirrhotic cardiomyopathy is a complex and not fully defined entity which has been connected to impaired myocardial contractile reserve to stress and altered diastolic relaxation. Aim of this study enrolling cirrhotic patients of different etiologies and stages, was to assess left ventricular (LV) systolic performance at rest through both "classic" echocardiographic indices and novel deformation-rotational dynamics parameters, trying to identify the pathophysiology of contractile dysfunction in cirrhosis.
Methods: Seventy seven male cirrhotic patients (mean age 54.4±9.7 years) and 20 healthy control subjects were prospectively enrolled. All subjects underwent standard echocardiography and subsequent offline analysis to evaluate LV ejection fraction (EF) (Biplane Simpson's rule), longitudinal strain and strain rate indices and finally LV rotation using speckle-tracking echocardiography.
Results: There were no significant differences between groups concerning age and body habitus parameters. The etiology of cirrhosis was viral in 28.6%, alcoholic in 39%, alcohol plus hepatitis in 6.4% and other etiologies in 26% of the cases. Twenty five patients (35.2%) were Class A, 39 (50.4%) Class B and 13 (16.9%) Class C of the Child-Pugh Classification with equal distribution of etiologies among classes. EF and stroke volume showed an incremental trend through evolution from Class A to Class C of cirrhosis (EF=64.6±5.7 in controls vs 71±9.5 in class A vs 71.2±7.1 in B vs 73±7 in C, p=0.002). The increase in LV output was not accompanied by an increase in longitudinal deformation (strain was -19±1.9% in controls, vs -20.1±5.3% in class A vs -21.3±2.6% in B vs -21±3.4% in class C, p=0.181) but it could be rather attributed to an increase in apical systolic rotation and accordingly in LV twist (LV twist was 13.0±3° in controls vs 14.9±5° in A vs 16.5±2.8° in B vs 18.2±2.9° in C, $p<0.0005$). Despite however increase in LV rotation, times to both basal and apical systolic rotations were significantly delayed (p=0,015 and p=0,017 accordingly). These results were not influenced by the etiology of cirrhosis or the presence or not of ascites.
Conclusions: Increased EF in cirrhosis could be attributed to increased LV torsion. Despite however "improved" rotation values at rest, there is a significant delay in succeeding peak systolic rotation, hampering also the consequent untwisting-diastolic period. This fact may be associated with attenuation of contractile reserve during stress-exercise in cirrhotic patients.

P5375 | SPOTLIGHT

The left ventricular twisting in space and time: the pathophysiology of 4d heart cycle in hypertrophic cardiomyopathy

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Purpose: The untwisting delay is now recognized as a distinctive trait for Hypertrophic Cardiomiopathy (HCM) thanks to 2D and 3D speckle tracking echocardiography (2DSTE and 3DSTE). However, it has never been related to the temporal evolution of Left Ventricular (LV) shape during heart cycle. This is possible thanks to the concept of homologous times in order to evaluate shapes of LV at comparable electro-physiological events. We test here the hypothesis that the untwisting-rate is significantly correlated with the shape of trajectories in time of the LV.
Methods: Here we compared healthy subjects (n=50) with patients affected by HCM (n=11). We used 3DSTE (Toshiba, Artida) allowing the manual digitization of homologous landmarks and the identification of homologous electrophysiological time frames. We analysed the shape of LV trajectory during heart revolution. We chose 9 homologous electrophysiological times, including R wave peak, end of T wave, end-systolic volume, mitral valve opening and Q wave peak, and we predicted LV shape at those times. A modified Geometric Morphometrics toolkit was used in order to detect differences in trajectories shape attributes.
Results: We found that healthy subjects have a faster untwisting (Fig. 1) during diastole for global untwisting-rate and in particular for 3 out 4 apical segments in comparison to HCM patients ($p<0.05$). The global untwisting rate was significantly related to the shape modifications of LV trajectory in time ($p<0.05$).

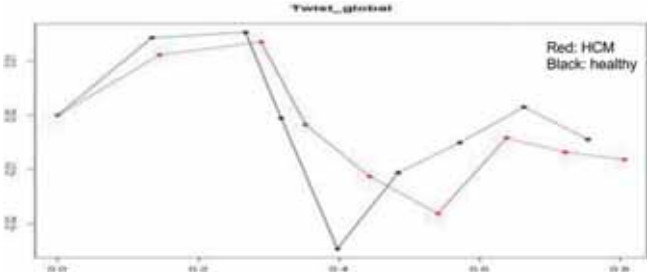

Figure 1. Untwisting rate trajectories.

Conclusions: As the untwisting is an important parameter for the evaluation of LV function, its significant correlation with the shape of LV motion trajectory in time could allow considering the trajectory analysis, in the near future, as a new potential pre-clinical diagnostic metric in HCM patients evaluation.

P5376 | SPOTLIGHT

Does timing matter for strain measurements?

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Current speckle tracking based strain measurements are highly automated. It remains often unclear, however, where a particular analysis software defines the zero-baseline and the systolic strain measurement position. This study was set-up to investigate, to which extend timing definitions influence strain measurements.
Methods: 30 subjects (10 healthy volunteers, 10 patients with ischemic heart disease and 10 patients with typical LBBB) underwent a complete echocardiographic exam. 2D strain images from the apical 4 chamber view were analyzed by a single reader. End-diastole (ED) and end-systole (ES) were defined as peak R and aortic valve closure (derived from CW Doppler), respectively. Using this reference, global (GLS) and segmental (SS) longitudinal end-systolic strain was measured. Measurements were repeated with changing the definition of either ED or ES by ± 4 frames. Resulting strain changes were expressed as absolute percentage of the reference value. The mean frame rate was 61/sec.
Results: Changing the definition of ED and ES resulted in significantly different GLS and SS values in all subjects. GLS was less affected than SS. Measurements in normals were least sensitive and those in dyssynchronous hearts most

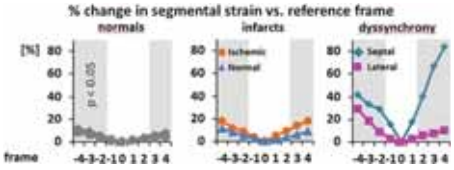

Figure 1

sensitive to changes in the definition of ED and ES. See figure (grey shaded areas indicate significant differences).
Conclusions: The exact temporal definition of end-systole and diastole has a major impact on accurate strain measurements. Particularly segmental strain in dyssynchronous hearts can vary up to 20% per frame. Manufacturers are asked to improve their respective software algorithms and users must take this into account when using speckle tracking strain clinically.

P5377 | BEDSIDE
Feasibility of a new hybrid imaging system featuring fusion of multislice coronary tomography and 3-D speckle-tracking echocardiography

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Background: Multislice coronary tomography (MCT) and 3D strain speckle-tracking imaging (3DS) are two of the greatest advances in cardiology imaging in the recent years. Their main limitation is the lack of integration of the information that they give separately, as MCT provides only anatomical data, and 3DS contributes exclusively functional information. We suggest that a new system featuring at the same time coronary anatomy and myocardial mechanics would overcome that limitation.
Objective: We tested a hybrid imaging software prototype capable of managing at the same time data from both MCT and 3DS, and displaying them as a single series of hybrid images. The aim was to test the feasibility of the system both with rest and stress 3DS echocardiography.
Results: 15 patients (11 male, 4 female) aged 56,1±9,9 with chest pain history and confirmed or suspected significant stenoses in MCT were included and underwent 3DS echocardiography at rest. 5 of them also underwent stress echocardiography by clinical indication. Abnormal regional contractility at rest was identified on 10 patients, and 3D-strain defects matched with the location of coronary stenoses in all cases. Fig.1 shows hybrid image in a patient with significant stenosis in LAD artery and low regional strain at the apex of left ventricle in the rest study. Stress 3DST showed ischemia in one patient, with perfect matching of one of the diseased vessels, and it discarded ischemia in four patients with uncertain lesions on CT.

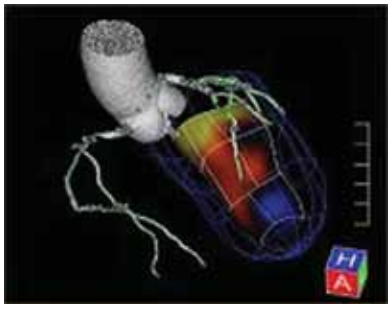

Figure 1

Conclusion: Hybrid imaging from MCT plus 3D myocardial mechanics is feasible from ordinary data obtained with both techniques separately and processed with a new software, either with resting or stress echocardiography. Clinical studies will test the usefulness of this approach.

P5378 | BEDSIDE
New tools to evaluate right ventricular evolution after heart transplantation

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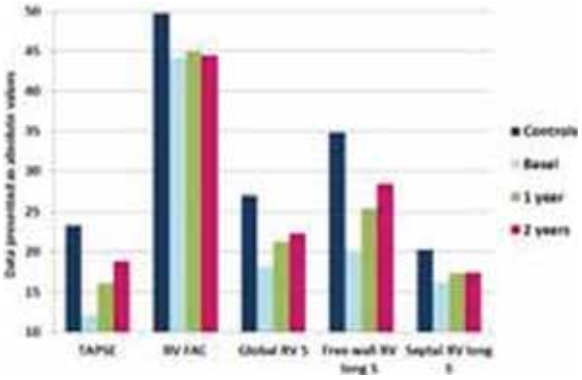
Right ventricular (RV) dysfunction commonly occurs after heart transplantation (HT). Its evaluation using echocardiography is limited due to geometric problems and its changes in post-HT patients have not been properly described.
Objective: To compare function and evolution of RV after HT with healthy controls.
Methods: We enrolled 29 patients followed at least 1 year (20 patients 2 years) and 24 healthy controls. TAPSE, RV fractional area change (FAC), Tei index and RV longitudinal strain (LS) were measured. Studies with biopsy rejection ≥2R were excluded.
Results: Results are shown in the table/figure.
Conclusions: Consistently with the relative loss of RV longitudinal contraction in the post–cardiac surgery subjects, TAPSE and RVGLS of HT patients were markedly reduced in the early postHT period, and both improved progressively during follow-up reaching normal values. RVFAC is nearly normal in early postHT and remains unchanged during the follow up. It could be considered the most accurate method to assess RV function in the eary postHT period.

Evolution of RV parameters

	TAPSE (mm)	RV FAC	Global RVS	Free wall RV long S	Septal RV long S	TEI index
Controls	23.3±4.0	49.7±7.9	–27.0±4.7	–34.8±9.6	–20.3±3.5	0.46±0.1
Basal	12.1±2.6*	44.1±9.6#	–18.1±3.4*	–19.9±4.5*	–16.2±3.8*	0.78±0.4*
3 months	14.9±3.8*	45.0±7.8#	–19.0±4.3*	–19.7±4.5*	–15.9±4.3*	0.71±0.3*
6 months	16.1±3.7*	43.7±9.3*	–20.2±4.2*	–24.4±5.8*	–16.7±4.1*	0.68±0.3*
1 year	16.1±4.2*	45.0±11.2	–21.3±4.6*	–25.4±7.1*	–17.3±5.0*	0.76±0.3*
2 years	18.8±4.1*	44.4±9.3	–22.3±3.8*	–28.4±6.3*	–17.4±3.3*	0.68±0.3*

*p<0.01, #p<0.05.



P5379 | BEDSIDE
Echocardiographic assessment of wall shear stress: association with the development of adverse remodeling after myocardial infarction

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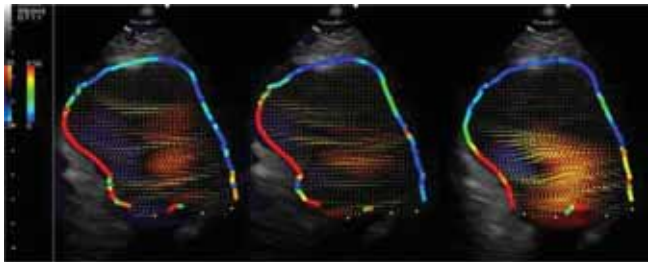
Introduction: Adverse remodeling after myocardial infarction includes the potential development of ventricular aneurysms. Wall shear stress (WSS) may have a determining role in this process. The goal of this study is to analyze, through advanced echocardiographic calculations, the association between the intensity of WSS and the presence of ventricular aneurysms.
Methods: Patients with intraventricular aneurysm underwent echocardiographic examination with Vector Flow Mapping (VFM), an advanced echo-modality capable of calculating flow-generated WSS from flow velocity variation next to the wall. WSS in the aneurysmatic area was analyzed and the size and shape (depth and width) of the aneurism were measured.
Results: 11 patients (10 males, aged 70.4±8.4, LVEF 43.8±10.5) were studied. Intensity of peak WSS throughout the cardiac cycle was graded on a 0-to-5 scale. A cut-off point of 4 was established to differentiate patients with intense (7, 63.6%) from those with moderate or mild (4, 36.3%) degrees of WSS. Patients with WSS ≥4 presented significantly deeper aneurysms (13.2±2.6 mm. vs. 7.9±2.1 mm., p<0.01) and a tendency to larger aneurysms (15.2±2.1 ml. vs. 12.1±2.5 ml., p=0.059) compared with patients with WSS <3. Additionally, none of the patients with WSS ≥4 presented thrombus inside the aneurysm (0/7, 0%), while 3 out of 4 (75%) presenting WSS <3 showed a thrombus inside the aneurysm.



High-intensity wall shear stress

Conclusions: The development of larger and deeper ventricular aneurysms in patients with ischemic cardiomiopathy seems to be associated with the presence of high levels of wall shear stress on the infarcted region. Additionally, patients with lower shear stress on the aneurysm are at higher risk of developing thrombi inside the aneurysmatic area.

P5380 | BEDSIDE

How could quantitative longitudinal peak systolic strain help in the detection of left ventricular wall motion abnormalities in our daily echocardiographic practice?

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Purpose: Transthoracic echocardiography (TTE) is the most commonly used tool for the detection of left ventricular wall motion (LVWM) abnormalities. Experienced cardiologists use visual evaluation, which is responsible for a high inter-observer variability. Automatic Function Imaging (AFI) provides segmental Longitudinal Peak Systolic Strain (LPSS) values and is more reproducible. However, AFI has not yet entered into routine. Hence, the role of segmental LPSS values in the prediction of LVWM in our in-hospital daily practice has not been fully evaluated.

Methods: We investigated how on-line segmental LPSS values could predict segmental LVWM. Echocardiograms were performed by a single sonographer in his daily clinical practice. LVWM was evaluated on-line and LPSS values calculated according to a 19-segments model, on apical 3-, 4- and 2-chamber views.

The analysis involved 507 consecutive and unselected TTE between Aug-2012 and Nov-2013. N=11154 segments were recorded. After excluding the apexes, 10647 segments entered the analyses. N=10590 segments were successfully tracked (99.5%). Segments were classified as normal (1), hypokinetic (2), akinetic (3), dyskinetic (4) and paradoxal (5, for the septum) and a segmental LPSS value was associated to each segment.

Results: Segmental LPSS values for normal basal/ normal median/ and normal apical segments were (mean; 95% Conf. Interv): -16.4%; -[16.6-16.2]%/-18.1%; -[18.3-17.9] % /and -21.1%; -[21.3-20.8] %, respectively, the difference being significant between the three. Segmental LPSS values for hypokinetic basal/hypokinetic median and hypokinetic apical segments were: -7.7%; -[9.2-6.3]%/ -10.1%; -[11.3-9.0]%/ and -8.9%; -[10.2-7.5]%, these three hypokinetic values being significantly different from the three normal values, but not significantly different from the other abnormal segments' LPSS values (akinetic, dyskinetic, and paradoxal).

Conclusion: On 10590 segments successfully tracked, LPSS values could differentiate normal from abnormal segments (eye LVWM abnormalities), but could not differentiate the different levels of abnormality. These results remain important in our daily echographic practice.

P5381 | BEDSIDE

Peroperative improvement in left ventricle longitudinal motion after transcatheter aortic valve implantation predicts better outcome

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Purpose: LV function is expected to improve immediately after transcatheter aortic valve implantation (TAVI) when afterload is reduced, but does not occur in all patients due to limited myocardial reserve. We hypothesized that peroperative improvement in systolic LV longitudinal motion after TAVI predicts better outcome.

Methods: 64 pts (mean age 81 (7) yrs) scheduled for TAVI were included. Transoesophageal 4 and 2ch echocardiograms were obtained immediately before and ~15 min after valve implantation. Peak systolic myocardial velocity (s') by tissue Doppler Imaging (TDI) was obtained from 8 basal segments, and averaged. Pts were predefined responders for improved systolic function if TDI s' increased ≥20% after the procedure. Outcome 3 months after TAVI was assessed by improvements in NYHA class, proBNP and systolic function (transthoracic s' (apical 4ch view)).

Results: 34 pts were classified responders and s' increased from 2.2 (0.8) to 3.1 (1.1) cm/s ($p<0.05$). In 29 pts s' remained unchanged at 2.4 (1.1) cm/s. Age, gender, preoperative NYHA class, proBNP, Euroscore and perioperative handling were similar in responders (R+) and non-responders (R–). Only responders had improved systolic function and reduced proBNP 3 months after TAVI accompanied with a significantly better NYHA class compared to non-responders (Fig. 1).

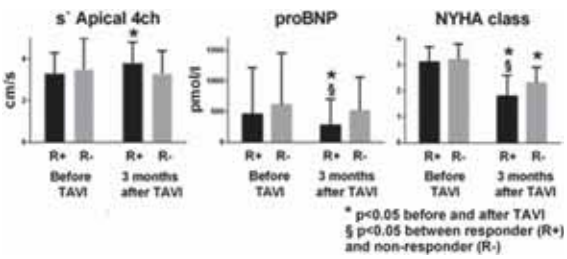

Figure 1

Conclusion: Immediate improvement in longitudinal s' during the TAVI procedure predicted better outcome after 3 months with improved systolic function, proBNP and NYHA class. Peroperative TDI may be used to identify pts with less favorable outcome after TAVI.

P5382 | BEDSIDE

The impact of myocardial ischemia on transmural mechanics using multi-layer speckle tracking echocardiography

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Purpose: Transmural variation in myocardial mechanics is dependent on the complex multi-layers of myocardial fibre orientation. Longitudinal myocardial contraction predominantly originates from the inner endocardial layer. We hypothesize that endocardial longitudinal strain is a sensitive marker of early myocardial ischaemia.

Methods: Thirty patients (mean age 68±8, EF 61±11%) underwent dobutamine stress echocardiography (DbE) as per clinical indication. Images were acquired between 50-80 frames/sec by 2D speckle tracking echocardiography at rest and peak dose DbE. Multi-layer peak systolic longitudinal (LongS) and peak systolic circumferential strain (CirS) analysis were measured from the inner endocardial (endo), mid, and outer epicardial (epi) layers using the latest GE EchoPAC BT13 post processing software. Myocardial ischaemia was defined as deterioration in wall motion score at peak dose DbE and correlated with significant coronary artery stenosis by coronary angiography.

Results: Of total of 480 segments, 362 were normal and 46 were ischaemic at peak dose. There was a transmural gradient of LongS (%) and CirS (%) from the endocardium to epicardium in normal segts at rest (LongS Endo -22.8±7.8, LongS Mid -19.8±6.0, LongS Epi -17.7±4.4, $p<0.0001$); (CirS Endo -32.8±10.9, CirS Mid -23.6±7.9, CirS Epi -17.4±6.4, $p<0.0001$). Endocardial LongS was the most sensitive marker for ischemia during DbE. Changes in all 3 layers of CirS could not differentiate normal from ischemic segts (Table).

Multi-layer LongS and CirS during DbE

Strain at Peak Dose (%)	Normal	Ischaemic	p value
LongS Endo	–24.3±13.7	–16.0±6.6	0.0001*
LongS Mid	–20.9±9.7	–15.3±5.7	0.0002*
LongS Epi	–17.9±7.2	–16.2±4.8	0.22
CirS Endo	–37.5±15.1	–33.0±10.7	0.06
CirS Mid	–26.6±11.2	–23.5±7.9	0.08
CirS Epi	–19.5±8.9	–17.2±7.1	0.11

Conclusions: LongS is superior to CirS in the detection of myocardial ischemia. This alteration in transmural myocardial mechanics is likely to reflect early subendocardial ischaemia.

P5383 | BEDSIDE

Automated Function Imaging (AFI)-derived strain rate evaluation of left ventricular relaxation

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Purpose: Global early diastolic peak strain rate (SRe) represents the mean early diastolic performance of all left ventricular (LV) segments and has been experimentally demonstrated to depend on LV relaxation. Speckle-tracking Automated Function Imaging (AFI) is a relatively simple method to measure echocardiographic longitudinal strain. We explored its potential to measure SRe in a large patient population.

Methods: We exmamined 427 consecutive patients with (339) and without (88) heart diseases (ranges, age: 14-93 y., HR: 40-130 bpm, systolic arterial pressure: 90-180 mmHg, biplane ejection fraction, EFb: 15-78%), using GE Vivid 7/9 systems (Echopac v112). AFI-derived peak maximum early diastolic SRe (s^{-1}) and time to peak SRe (SRetp, ms) were obtained in the 3 apical views from the first derivatives of the strain curves and averaged.

Results: Peak SRe and SRetp were normally distributed and respectively 1.86±.83 s^{-1} (95% CI 1.68, 2.03) and 153±42 ms (95% CI 144, 162) in normals and 0.98±0.6 and 187±76 in patients (both, $p<0.001$). They were both decreased in dilated cardiomyopathy (n=35; 0.55±0.28, 245±86; $p<0.001$), CAD with normal preload (n=30; 0.71±0.51, 201±72; p=0.001), and aortic stenosis (n=23; 0.9±0.38, $p<0.001$; 163±38, p=ns); there was a trend towards an increase in SRe in athletes (n=12; 2.34±0.86). At multiple regression analysis, adjusted for LV preload, mitral regurgitation, filling pressures, stroke volume and left atrial volume, SRe was positively determined by tissue Doppler peak systolic mitral annulus velocity, and negatively by age, LV wall motion score index, mass index, heart rate and mitral E wave deceleration time ($r=0.74$, $p<0.001$), whereas SRetp was positively determined by LV wall motion score index, mitral E wave deceleration time, and systolic pulmonary pressure, and negatively by heart rate ($r=0.6$, $p<0.001$). When LV isovolumic relaxation time was set as the dependent variable, it was determined negatively by tissue Doppler peak early

diastolic mitral annulus velocity, heart rate, and LV filling pressures, and positively by SRetp (r=0.69, p<.0001). Notably, SRe was greatly reduced in all grades of LV diastolic dysfunction (DD): no DD, 1.67±.8 (95%CI 1.56-1.78); grade I DD, 0.79±0.44 (95%CI 0.72-0.86); grade II DD, 0.7±0.58 (95%CI 0.33-1.07); grade III DD, 0.67±0.23 (95%CI 0.55-0.78); all p<0.001.
Conclusions: AFI-derived SRe and SRetp are both related to LV relaxation and its determinants. Unlike tissue Doppler velocities of the mitral annulus, they reflect global LV relaxation, and appear clinically promising, although presently not measurable "online".

P5384 | BEDSIDE
Can global longitudinal strain predict left ventricular ejection fraction in echographic daily practice?

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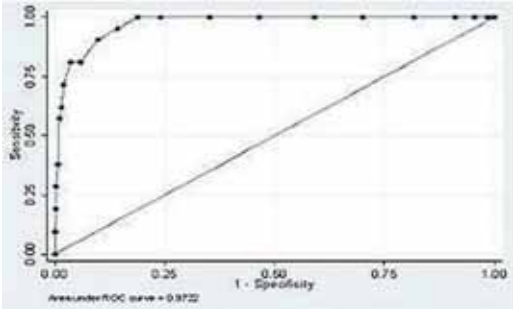
Purpose: Transthoracic echocardiography (TTE) is the most commonly used tool for the evaluation of left ventricular ejection fraction (LVEF). Its reproducibility remains a matter of controversy. Speckle tracking allows the assessment of left ventricular (LV) systolic function, by the measurement of Global Longitudinal Strain (GLS). It is more reproducible. However, GLS has not yet entered into routine. Hence, its role in the prediction of LVEF has not been fully evaluated.
Methods: On 507 consecutive unselected TTE (excluded N=53), we investigated how on-line 2-dimensional GLS could predict LVEF (biplane Simpson method). Simple linear regression was used to assess the relationship between LVEF and GLS. The tests were repeated for each class of echogenicity (good, moderate, poor). ROC analyses was used to identify the threshold of GLS that predicts LVEF ≤40%.
Results: The most frequent indication for TTE was stroke (N=235). Median LVEF (Inter Quartile Range, IQR) was 65% (59-70) and median GLS (IQR) was -19% ([-21]-[-16]). A correlation was found between LVEF and GLS in the whole series (N=507), with r=0.53 (p<0.0001), and LVEF = -1.45GLS+38.04 GLS. For poor echogenicity (N=76), r=0.53 (p<0.0001) and LVEF= - 1.48 GLS+41.65, where GLS explained 26.6% of LVEF variation, and for one unit decrease in GLS, we would expect a 1.48 unit increase in LVEF. When echogenecity was moderate (N=187) or good (N=244), the correlation was better. The area under ROC curve was 0.97 and GLS ≥-14% allowed to detect LVEF ≤40% with a sensitivity of 95% and a specificity of 86%.



ROC analyses: prediction of LVEF ≤40%.

Conclusion: GLS is easy to obtain and accurately detects LVEF ≤40% in unselected patients. It may especially be helpful when echogenicity is poor.

P5385 | BENCH
Predictors of mortality and/or transplantation in patients submitted to echo guided CRT optimization

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Introduction: Cardiac resynchronization (CRT) is a therapy for patients (pts) with low ejection fraction (EF) (<35%), electrical dyssynchrony and heart failure. 25-30% do not respond clinically and 35-65% do not obtain left ventricular (LV) reverse remodeling.
Objective: To analyze retrospectively pts submitted to echo guided CRT optimization (OP) after implantation (IMP) and review the results and predictors of mortality or heart transplantation (HTX).
Methods: Clinical (etiology, age, gender, rhythm, time delay from IMP to OP and follow up after OP) and echocardiographic data (LV end diastolic and end systolic diameters and volumes, (LVEDD, LVESD, LVEDV, LVESV) EF, left atrial dimension, dysynchrony parametrers (Pitzalis, inteventricular mechanical delay, lateral or posterior delays with TSI, all segments and basal maximal delays and standard deviations with multiplane TSI) and other parameters (E/e', E/A, pulmonary artery systolic pressure, PASP) were analyzed. The revision of mortality was complete. OP was based on iterative method with analysis of Doppler LV inflow and outflow while AV and/or VV delays were changed. Pts were divided into 2 groups according to the absence (GI) or presence of major adverse events (death or HTX) (GII).
Results: 63 pts (42 male, mean age 63±11 years, EF pre IMP 24.6±5.5%, pre OP 29.0±9.6%, performed 11.3±19 months thereafter. 52 were in sinus rythm, 53 had previous LBBB, 14 had previous mitral regurgitaion >II/IV. 35 were dilated cardiomyopathy, 25 ischemic. AV was modified in 45 pts, VV in 40 (both in 22). OP was repeated once in 10 pts and twice in 2 pts, 15 pts (23.8%) belonged to GII. Global mortality was 21% and 2 pts were submitted to HTX. LVESD pre IMP was greater in GII (p<0.05). e' velocities were lower and E/e', max delay, posterior delay, all segments and basal standard deviation were higher pre OP in GII (p<0.05). At 6 months of FUP there was also a difference between the 2 groups in what concerns: EDD, ESD, PASP, E/Vp, E/e' (all p<0.05). No parameter during OP was related to outcome.
Conclusion: Pts submitted to VV and/or AV OP after CRT have a bad prognosis: MACE in 24% after 31 months of follow up. More dilated ventricles preimplantation and pre OP were related to worse outcome and the presence of residual significant dyssynchrony and worse LV function (EF and E/e') before OP were relevant for prognosis. After OP the greatest predictors of outcome were enlarged ventricles, and residual significant diastolic dysfunction. The imediate changes obtained during OP were not significantly related to prognosis.

NEW INSIGHT IN DOBUTAMINE STRESS ECHO

P5387 | BEDSIDE
The novel index of contractile function: shape of dynamics's curve of cardiac output during dobutamine stress echocardiography

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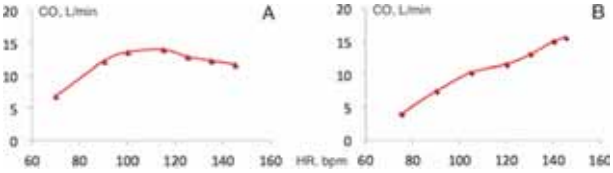
Purpose: The purpose of study was to examine of myocardial contractile reserve (MCR) by novel index of contractile function.
Methods: 66 patients with heart disease and with (n=51) or without (n=15) heart failure were studied during dobutamine stress echocardiography with characterization of MCR by Doppler imaging. Measured rest echo parameters, brain natriuretic peptide (BNP) and Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores were assessed in all the patients. During the stress test with the help of continuous wave Doppler the blood flow in the ascending aorta was registered. Value of cardiac output (CO) during the stress test was calculated every 10-20 bpm increase. All patients were separated into two groups. Group A (n=33) were patients with decreased MCR and byphasic dynamics of CO (figure, curve A). Group B (n=33) were patients with normal MCR defined as an increment of CO up to submaximal HR and monophasic dynamics of CO (curve B).
Results: The two groups statistically significant (p<0.05) differed for the end-diastolic volume (174,3±94,2 mL in group A vs 110,2±41,5 mL in group B), end-systolic volume (110,6±87,6 mL in group A vs 53,1±34,7 mL in group B), ejection fraction (EF) (44,9±18,7% in group A vs 54,3±13,7% in group B), BNP level (109,5±78,9 pg/mL in group A vs 34,5±39,3 pg/mL in group B) at rest; the CO at load-peak (6,93±2,32 L/min in group A vs 8,02±3,33 L/min in group B); and MLHFQ scores (19,6±23,9 in group A vs 4,8±11,3 in group B).



CO dynamics during stress test.

Conclusions: MCR is a measure of the ability of the myocardium to increase its contractility with stress. The normal response is an increase CO up to submaximal HR in the form of monophasic curve of CO. Appreciation of the MCR will better inform optimal design for diagnostic and therapeutic strategies.

P5388 | BEDSIDE
The medium term prognostic value of dobutamine stress echocardiogram in patients with high risk scores of coronary artery disease according to NICE clinical guideline 95

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Coronary artery disease (CAD) is an important differential diagnosis of chest pain. The 2010 NICE Clinical Guideline 95 (CG95) recommends investigating the complaint of chest pain by stratifying patients' CAD risk according to the modified Diamond Forrester criteria. Patients possessing high (61-90%) CAD risk should receive invasive coronary angiography (CA) as first line investigation. However, a significant proportion of these patients will instead receive dobutamine stress echocardiography (DSE), which is recommended for moderate risk patients. A negative DSE in high risk patients will be considered as negative for significant CAD, but the prognosis of these patients, who are usually discharged from cardiology follow up, is unclear. This study aims to assess the prognosis of high CAD

risk patients following a negative DSE in the first two years following implementation of NICE CG95.
In this retrospective study, we identified high CAD risk patients who were referred for DSE from the rapid access chest pain clinic (RACP). We clarified the reasons why patients were not referred for CA. Patients with negative DSE were followed up via the hospital's electronic record system, which contains all clinical information including inpatient and outpatient attendances, clinical letters, test results, and date of death.
504 patients were referred for DSE from the RACP between September 2010 and August 2012. 164 patients possessed high risk for CAD. 52 were referred based on patient choice, 54 based on clinical assessment, and 7 had contraindications to CA. 117 high risk patients had a negative DSE; these cases were followed up for a median of 21 months. 4 (3.4%) high risk cases had persistent cardiac symptoms requiring additional hospital review and investigations following a negative DSE, of which 1 case (0.8%) had significant CAD identified on angiography requiring percutaneous coronary intervention. The remaining 113 (96.6%) were free from significant clinical complaints requiring hospital attendance.
In the first 2 years following the implementation of NICE CG95, we identified a significant number of high CAD risk patients who were offered DSE. The reasons for selecting DSE over conventional angiography were due to the clinician's judgement of appropriateness and patient choice in equal parts. The medium term outcome of those who have had a negative DSE is favourable, with only a few ($<$5%) requiring additional cardiac investigation and 1 case ($<$1%) of significant coronary disease. Thus, a negative DSE is a reliable objective indicator of good prognosis in patients with high risk of CAD in a chest pain clinic.

P5389 | BEDSIDE
Relative wall thickness is associated with subendocardial dysfunction during dobutamine stress echocardiography

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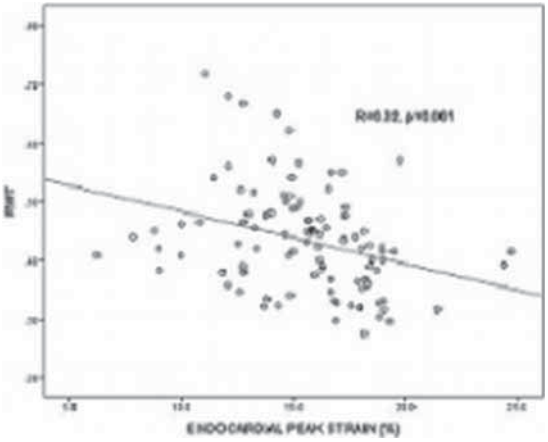
Purpose: ST segment depression (STD+) on stress ECG and a hypertensive response to stress (HR+) are known markers of adverse prognosis. To address whether STD+ and HR+ may be related to subendocardial ischaemia in individuals without inducible regional wall motion abnormalities during stress (RWMA), we investigated the significance and myocardial consequences of these abnormal findings (STD+ or HR+) using echocardiographic strain as a marker of myocardial tissue deformation.
Methods: In this cross-sectional study of 100 low cardiovascular risk pts (age 61$\pm$13 yrs; 59% male) without inducible RWMA during DSE, we studied 25 consecutive STD+ pts ($>$1mm horizontal ST-depression on ECG) and 25 consecutive HR+ pts (SBP $\geq$180mmHg at peak), compared with 50 randomly selected controls without STD+ or HR+. Using velocity vector imaging (VVI), longitudinal endocardial and epicardial peak global strain (PS) in 12 basal and mid-cavity myocardial segments were averaged from 3 apical views at rest and peak stress. LV mass, volumes and EF were calculated according to EAE guidelines.
Results: Demographics, LV volumes and EF, mass and relative wall thickness (RWT) were similar between groups. Although STD+ and HR+ groups had higher resting SBP than controls, there were no differences in resting endocardial or epicardial PS between the 3 groups. At peak stress, epicardial PS was similar in all groups, but endocardial PS in STD+ (-14$\pm$3%) and HR+ groups (13.1$\pm$4%) was lower than controls (-17$\pm$3, p$<$0.01). In a multivariable model (R2=0.25, p$<$0.01), ST depression (B=-0.31, p$<$0.01) and RWT (B=-0.27, p$<$0.01) [figure], but not LV mass were correlated with endocardial PS.



RWT & peak strain correlation.

Conclusions: Pts with stress-induced STD+ or HR+ have impaired subendocardial function, which is associated with increased RWT rather than LV mass.

P5390 | BEDSIDE
Stress echocardiography and long-term prognosis in patients after successful primary percutaneous intervention and incomplete revascularization of non-culprit lesions

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Background: Stress echocardiography is important noninvasive tool for the detection of myocardial ischemia. Nevertheless its role in risk stratification after primary percutaneous intervention (pPCI) has been incompletely documented. Aim of this study was to assess prognostic value of stress echocardiography after successful pPCI for acute myocardial infarction (AMI). Also, we sought to evaluate prognostic value of heart rate recovery (HRR) in stable coronary artery disease.
Methods: Our study comprised of 104 patients successfully treated with pPCI. All patients performed stress echocardiography according Bruce protocol in order to assess residual ischemia in coronary artery other than treated vessel. Stress echocardiography was considered positive for ischemia in the case of new or worsening of preexisting wall motion abnormalities. Duke treadmill score, wall motion score index (WMSI) at rest as well as HRR in the first minute after exercise was calculated in all patients. Lesion severity of on culprit coronary arteries was assessed by quantitative coronary angiography. All the patients were followed for the occurrence of hard cardiac events: cardiac death, myocardial infarction and coronary artery bypass graft (CABG) intervention.
Results: Out of 104 patients 14 patients had positive stress echo test and they were scheduled for elective PCI, remaining 90 patients were included in the study (59 male, 31 female). The average age was 56$\pm$9 years. During the follow up period (mean 44$\pm$13 months) hard cardiac events occurred in 9 patients with negative stress echocardiography (3 deaths, 3 myocardial infarcts, 3 CABG). There was statistically significant difference between patients with and without hard cardiac events regarding Duke score (p=0.019) and HRR (p=0.027), but there was no difference in diameter stenosis (p$>$0.05) and WMSI at rest (p=0.803). Patients with lower Duke score and lower HRR had more hard cardiac events. Area under receiver operating characteristic curve for Duke score was 0.774 with cut off value of 5.5 (Sn 82%, Sp 75%) and for HRR was 0.674 with cut off value of 33 heart beats.
Conclusions: Negative stress echo test after successfully pPCI in patients with incomplete revascularization had excellent negative prognostic value for the occurrence of the hard cardiac events. Whereas HRR as well as Duke treadmill score can further stratify risk in these patients.

P5391 | BEDSIDE
Does a method to increase appropriately indicated exercise echocardiograms exist?

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Background: The burden of diagnostic tests requested without an appropriate indication is remarkable because it means an unnecessary use of limited resources. As a result of this, the ASE has defined the appropriate use criteria for echocardiography in 2011. Our aim was to increase the number of exercise echocardiograms (EE) with an appropriate indication using a simple intervention.
Methods: We collected all the EE request forms that arrived at our institution – a tertiary hospital- between August 2012 and April 2013. We assessed each of these forms following the 2011 ASE use criteria and determined if they were "appropriate", "uncertain", "inappropriate" or "unclassifiable". On February 26th 2013 we gave a lecture on EE technique and use criteria. All the cardiologists of our institution (potential EE requesters) were invited and also, in order to reinforce the intervention, they were sent an email with handy diagrams enclosed to make their every day decisions easier. We compared the EE requested before the lecture (August 2012 to February 2013) to the EE requested after it (March and April 2013) to estimate the effect of our intervention.
Results: We assessed 232 EE request forms, 176 of which belonged to the pre-intervention period: 133 appropriate (75,6%), 26 inappropriate (14,8%),15 uncertain (8,5%) and 2 unclassifiable (1.1%). 56 request forms belonged to the post-intervention period: 50 appropriate (89,3%), 3 inappropriate (5,4%), 1 uncertain (1,8%) and 2 unclassifiable (3,6%). The appropriate EE percentage was significantly higher after intervention than before it: Risk Difference 14% (Confidence Interval of 95%: 24% to 3%) and Odds Ratio 2,7 (p=0,029). We did not find significant differences between groups in age (61,2 vs 63,7 years), sex (67% vs 70% male), left bundle branch block (8% vs 9%) or left ventricle ejection fraction (59% vs 57%). The most common indication settings were those related to symptomatic ischemic heart disease and did not change with intervention: "evaluation of ischemic equivalent nonacute" (24% vs 29%, p=0,6) and "postrevascularization " (18% vs 21%, p=0,7).
Conclusions: The percentage of EE that are requested following an appropriate indication in our hospital is acceptable (75,6%). A simple intervention (lecture and email reminder) significantly improved this percentage without affecting the prescription profile.

P5392 | BEDSIDE
Paralympics respond differently to exercise load with respect to the presence of spinal cord injury. A stress echo study

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Objective: Athletes with spinal cord injuries (SCI) have different exercise physiology from other Paralympics: preload cannot be adequately increased, which limits exercise capacity. We evaluated the response of left ventricular (LV) and right ventricular (RV) function to exercise with respect to the type of injury.
Methods: We studied 13 SCI and 34 non-SCI athletes, age 30.7±9.5 years, 17% female, body mass index (BMI) 25.7±7.2, years in elite sport 7.6±6.
We performed an echocardiographic exam at rest and after physical stress. Workload with stepper was 6121.2±1356.3 grm. For wheel-chair athletes we used dumbbell (3.8 kg) reps.
Results: SCI-athletes were older and had smaller BMI, LV end-diastolic diameter and LV mass index and decreased baseline LV twist values; RV dimensions and other LV and RV functional parameters didn't differ between groups.
Heart rate (HR) increased significantly during exercise in non-SCI-athletes but with borderline significance in SCI-ones – table 1. Maximal HR was higher in non-SCI compared to SCI-athletes (p=0.003). After exercise SCI-athletes had improvement in LV deformation indices and LV diastolic function, while LV twist didn't increase significantly. RV function improved only during isovolumic contraction, while functional parameters during ejection did not respond to exercise.
In contrast, non-SCI-athletes showed improvement of RV systolic indices after exercise (exception was RVGLS). LV systolic response to exercise paralleled that of SCI-athletes, but diastolic function wasn't affected.

Exercise response in SCI/non-SCI athlet

Parameter, mean ± SD	SCI athletes		p	Non-SCI athletes		p
	baseline	exercise		baseline	exercise	
Heart rate	59±6	97±19	0.05	68±14	137±20	0.001
LV deformation GLS (%)	–20.1±2.5	–23.4±3.4	0.003	–19.8±2.2	–23.1±2.8	<0.001
GLSR (s^{-1})	–1.12±0.16	–1.47±0.33	0.003	–1.13±0.17	–1.61±0.42	<0.001
LV E/e'	7.4±1.7	6.4±1.5	0.013	6.1±1.2	6.5±1.2	ns
LV twist (°)	6.3±8.4	10±6	ns	14.4±6.3	16.9±9	ns
RV S' (cm/s)	11.1±1.5	14.9±3.2	ns	13±2.4	18.3±5.6	<0.001
RV IVA (cm/s^2)	2.9±1.1	5.6±2.8	0.001	3.4±1.1	6.2±2.4	<0.001
RV deformation GLS (%)	–29.9±6.4	–33.2±6.2	ns	–27.6±6.9	–28.3±13.2	ns
GLSR (s^{-1})	–2.42±0.54	–3.35±0.72	ns	–2.18±0.75	–3.19±1.12	<0.001

Conclusion: Paralympics with SCI show impaired RV response to exercise compared to non-SCI-athletes, probably related to decreased sympathetic drive (HR response and preload changes). Whether this has a protective or damaging effect on RV, remains to be elucidated.

P5393 | BENCH
Outdoor stress echo: identification of extreme lung by chest sonography

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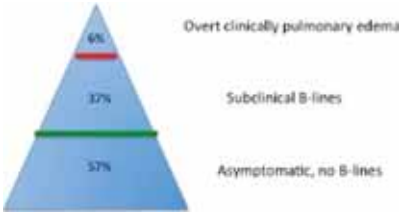
Purpose: Subclinical pulmonary edema, detectable as B-lines by lung ultrasound (LUS), can occur during extreme situations of strenuous efforts in ordinary environment or ordinary effort in extreme (underwater or high altitude) environments.
Methods: We performed LUS with transthoracic probe in 155 healthy and fit subjects (44 females, mean age 41±9 yrs): 71 Iroman and ultra marathon runners, 53 high altitude (between 3.880 m s.l. and 5.050 m s.l.) trekkers, 31 elite apnea divers (diving depth 31 to 112 m). The studies took place outdoor by portable echo in Sahara desert, Elba Island (triathletes), Red sea (apnea divers), Nepal and Monte Bianco (trekkers)
Results: B lines (absent at baseline) were present (>10) in 57 subjects during or after the extreme condition exposure. In 9 subjects (6%) the B lines were harbinger of clinically overt pulmonary edema (cough, and/or pulmonary crackles, and/or haemoptysis) (see figure)



Conclusions: Out-door stress echo with portable ultrasound machine allows to detect subclinical (sometimes progressing to overt clinical) pulmonary edema in super fit subjects performing extreme effort in ordinary environment and after ordinary efforts in extreme conditions. The "extreme lung" (physiological?) adaptation up to overt life-threatening pulmonary edema can be easily detected by LUS.

P5394 | BEDSIDE
Dobutamine-induced changes of multidimensional cardiac deformation predict functional capacity in patients with severe systolic heart failure

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Background: We investigated the dobutamine-induced changes of left ventricular (LV) multidimensional deformation and their relation to functional capacity of patients with severe chronic systolic heart failure.
Methods: In 100 patients with advanced heart failure, we performed a low dose dobutamine echocardiography study, including speckle tracking imaging. The patients' functional capacity was determined by the distance (m) during a 6-min walk test. Brain Natriuretic Peptide (BNP) was also measured.
Results: Dobutamine infusion increased LV ejection fraction (EF), LV outflow track velocity time integral (LVVTI), global longitudinal, circumferential, radial strain and strain rate ($p<0.05$). Resting values and dobutamine-induced changes of conventional 2D echocardiography markers, including EF and LVVTI, failed to discriminate the patients' functional capacity as assessed by a distance in 6min walk test >265m (median of our cohort) (p=ns). The dobutamine-induced changes (Δ) in longitudinal strain and strain rate were the best predictors of 6-min walk test>265m (areas under the ROC curve of 70% and 73% respectively, $p<0.05$) with an independent and additive predictive value in a model including age, sex, resting LVEF, LVVTI, longitudinal strain (or strain rate), ΔEF, ΔLVVTI (as measures of contractile reserve), BNP and type of cardiomyopathy (model x2=81.06 increased to x2=95.15 and x2=81.17 to x2=100.3 after inclusion of Δlongitundinal strain and strain rate, respectively, p for change <0.001)
Conclusion: In severe chronic systolic heart failure, the longitudinal, circumferential, and radial deformation are increased following dobutamine infusion. The dobutamine–induced changes of longitudinal myocardial deformation but not of conventional echocardiographic indices of LV function may discriminate the patients' functional capacity.

P5395 | BEDSIDE
Enhancing patient selection for coronary angiography thorugh the use of carotid ultrasound plaque quantification combined with stress testing as a screening tool

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Purpose: Determine if addition of carotid ultrasound to stress testing enhanced sensitivity for prediction of significant CAD and improved selection for angiogram.
Methods: Carotid ultrasound was performed on 320 consecutive outpatients undergoing same-day angiography. 209 patients had recently received at least one imaging based stress test and were selected for analysis. Mean far distal carotid intima-media thickness (CIMT) and maximal plaque height were measured and compared to angiographic scores for prediction of significant CAD. Significant CAD was defined as presence of at least one major epicardial coronary vessel with ≥50% luminal narrowing. Literature threshold values for increased CIMT (≥0.8 mm) and plaque definition (≥1.5 mm) were used for stratifying patients as low or high risk CAD. Stress test and ultrasound results, alone or combined, were analyzed for accuracy in stratifying patient risk of CAD.
Results: Adding maximum plaque height, measured by carotid ultrasound, to stress testing increased the negative predictive value (NPV) from 28% to 71%, and the sensitivity from 78% to 99%. Stress test/carotid ultrasound combination testing would have re-stratified 34/36 patients from low risk to high risk as confirmed by angiography.

Table 1

Test (N=209)	Result	Presence of significant CAD (≥50%)		Absence of significant CAD (<50%)		PPV	NPV	Sensitivity	Specificity
Stress test	+	TP	104	FP	55	65%	28%	74%	20%
	–	FN	36	TN	14				
CIMT	≥0.8 mm	TP	93	FP	34	73%	43%	66%	51%
	<0.8 mm	FN	47	TN	35				
Plaque height	≥1.5 mm	TP	130	FP	35	79%	77%	93%	49%
	<1.5 mm	FN	10	TN	34				
Stress test + CIMT	+	TP	130	FP	62	68%	41%	93%	10%
	–	FN	10	TN	7				
Stress test + plaque	+	TP	138	FP	64	68%	71%	99%	7%
	–	FN	2	TN	5				

Conclusion: In patients undergoing stress testing, CIMT and carotid plaque improved identification of significant stenosis. Carotid plaque quantification significantly improved the NPV of stress testing suggesting this is a practical tool to rule out significant CAD and enhance selection of patients for angiography.

P5396 | BEDSIDE

Combined analysis of myocardial function, viability and perfusion in patients with chronic total occlusion in relation to angiographic collateral flow

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Purpose: Indications for revascularization in chronic total occlusion (CTO) of the coronary artery depend on the interplay between myocardial function, viability and inducible ischemia. Technical feasibility of the procedure often relies on the angiographic collateral flow to the occluded artery. The aim of the study was to comprehensively assess these two aspects of qualification for the revascularization procedure.
Methods: The study included 54 patients (mean age 63 years, 85% males) with CTO referred for cardiovascular magnetic resonance to assess indications for revascularization. All patients underwent stress perfusion cardiovascular magnetic resonance imaging with means of dipyridamole. The presence of well-developed collateral flow was defined as a collateral connection grade=2 and Rentrop score=3.
Results: In the whole group, wall motion score index (WMSI) of the segments supplied by the CTO correlated with infarct size (rho=0.631, $p<0.001$) and the size of reversible perfusion deficit in that area (rho=0.284, p=0.04).
The presence of well-developed collaterals (n=24, 44%) was less likely related to systolic dysfunction of the segments supplied by the occluded artery (mean WMSI 1.31±0.44 vs. 1.64±0.67, p=0.04) in comparison to lack of well-developed collaterals. Patients with well-developed collaterals had a lower frequency of previous myocardial infarction of the CTO zone (38% vs. 67%, p=0.03), but had similar frequency of transmural infarctions (21% vs. 23%p=0.83). They less frequently presented perfusion deficits of the CTO area during hyperemia (42% vs. 70%, p=0.03) and the size of deficits was smaller (median 0.0% [interquartile range 0-12%] vs. 7.5% [0-15%] of the left ventricular mass, p=0.04].
Conclusions: Systolic dysfunction of the segments supplied by the occluded artery is related to both reversible (due to ischemia) and irreversible injury (previous infarction). Left ventricular segments supplied by CTO with well-developed collaterals are less prone to inducible ischemia; have smaller size of ischemia and better systolic function in comparison to those supplied by CTO with poor collateral circulation. This may potentially translate into smaller benefits of retrograde CTO revascularization, where good collateral flow is crucial for technical execution of the procedure.

MULTIMODALITY IMAGING IN VALVULAR HEART DISEASE AND AORTA

P5398 | BEDSIDE

Role of Doppler echocardiography and tissue Doppler imaging in predicting thromboembolic events in rheumatic mitral stenosis and normal sinus rhythm

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Purpose: Rheumatic mitral stenosis (MS) predisposes to left atrial (LA) thrombus formation and subsequent embolization. A strong body of evidence recommends anticoagulant therapy in the setting of atrial fibrillation (AF). However, there is no solid evidence when to start anticoagulation in MS and normal sinus rhythm (NSR). Tissue Doppler imaging (TDI) is an echocardiographic modality that demonstrates tissue velocities. LA wall fibrosis and hypertrophy secondary to rheumatic MS can be reflected on LA as well as appendage (LAA) wall velocities derived from PWD-TDI.
We examined TDI derived velocities as predictor of thromboembolic events in MS and NSR.
Methods: Our study included 79 patients with rheumatic MS in NSR. Case group (n=36) included patients with history of prior embolic events; while control group (n=43) included patients without history of embolization. All the studied population underwent history taking, clinical examination and ECG to rule out AF and confirm manifestations of embolization in the case group. Patients with CVS underwent bilateral carotid duplex to rule out Carotid artery stenosis. All patients underwent both transthoracic (TTE) and transeosophageal (TEE) echocardiogram. TDI of LA wall was done in the apical four chamber view yielding quadriphasic pattern as follows: Atrial contraction (AC) wave, atrial relaxation (AR) wave, systolic forward motion (SFM) wave and diastolic backward motion (DBM) wave. The waves were related to the simultaneously recorded electrocardiogram (ECG). Using TEE, we recorded PWD velocities at the LAA mouth as well as TDI of the LAA lateral wall. PWD revealed triphasic waves: Early and late emptying waves (positive waves) and filling wave (negative). TDI derived waves revealed the same triphasic pattern. The LA spontaneous echo contrast (SEC) was graded according to its density.
Results: Female gender predominated the studied group (83.7%). Both groups were age and gender matched. All patients were neither diabetic nor hypertensive. Both groups had comparable degree of MS. Waves derived from LA wall TDI did not show significant difference between the two groups. The LAA late emptying wave velocity (LAAeV) was significantly lower in the case group (p=0.004). The Dense SEC was negatively correlated with LAAeV as well as the TDI-derived LAA late systolic wave (LSW) velocity (r = -0.536, $p<0.000$ and r = -0.277, p=0.013 respectively).
Conclusion: LAA PWD as well as TDI reflect LAA function and flow states quantitatively. LAAeV and TDI derived LSW velocity may predict LA thrombus formation and subsequent embolization in MS and NSR.

P5399 | BEDSIDE

Transesophageal echocardiography in tavi without balloon pre-dilation: experience of a single center

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Purpose: Transcatheter aortic valve implantation (TAVI) is an alternative therapy in high-risk patients with severe aortic stenosis. Balloon pre-dilation is still a common procedure for valve preparation, however, TAVI without pre-dilation has been described as a feasible and safe procedure. The aim of this study is to show the usefulness of transesophageal echocardiography (TEE) during the patient selection and TAVI procedure guidance to aim a high success rate with minimal complications.
Methods: 63 patients with severe aortic stenosis not considered candidates to surgical treatment were sent for TEE evaluation prior to TAVI. After 2D and 3D TEE evaluation and measurement of aortic annulus and root, mobility of valve cusps, orifice characteristics and valve area, degree of calcification of the valve and aortic regurgitation, patients were considered, according to our criteria whether or not favorable for TAVI without pre-dilation.
Results: Mean age was 82±5 years. Mean aortic valve area was 0.61±0.16cm^2 and mean aortic annulus diameter was 2.2±0.25cm. Edwards Sapien prosthesis were implanted in 62% (n=39), some degree of paravalvular leakage was seen in 62% of patients (n=39) and only 22% (n=14) required post-dilatation due to regurgitation grade ≥3. Only 1.6% (n=1) of patients had severe paravalvular regurgitation that required a second intervention. Permanent pacemaker was needed in 6% of patients (n=4). No clinical embolisms were observed during the procedure and the follow-up.

Criteria for TAVI without pre-dilation

Favorable for TAVI WPD	Non-Favorable for WPD
Valve area >0.4cm^2	Valve area <0.4cm^2
Central orifice	Eccentric or Torn orifice
Calcification < grade 3	Calcification ≥ grade 3
Non-LVOT calcification	LVOT calcification
Absence of calcium nodules*	Calcium Nodules*
AR < grade 3	AR ≥ grade 3

Conclusions: The proper assessment of aortic annulus diameter, distribution of calcium, mobility of the leaflets and characteristics of the residual orifice with TEE allows to select patients with the ideal conditions for TAVI without balloon pre-dilation. Using these criteria is possible to obtain a high rate of procedure success with a minimal percentage of complications.

P5400 | BEDSIDE

Mitral valve and left ventricular reverse remodeling after surgical repair of submitral left ventricular aneurysms assessed with multi-slice computed tomography

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Purpose: Surgical repair of submitral aneurysms may present a technical challenge especially if the mitral valve (MV) apparatus is involved. We present the center surgical experience with the potential of multi-slice computed tomography (MSCT) in assessment of changes of MV and LV geometry and aneurysm morphology.
Methods: Between 05/06 and 12/13, 24 patients (m:w=20:4, ages 38-78, mean 62.3 years; mean NYHA class 2.91) with submitral LV aneurysm were operated upon. Echocardiography and MSCT were performed before and a short time after surgery. LV and aneurysm end-diastolic/end-systolic, stroke volume and aneurysm defect area (ADA) were measured and indexed to body surface area (LV-EDVI/LV-ESVI, A-EDVI/A-ESVI, SVI, respectively). LV ejection fraction (LVEF) and cardiac index (CI) were calculated on the basis of MSCT data. MV geometry was characterized by intercommissural and anteroposterior MV annulus diameter (ICD and APD respectively), MV annulus area (MVAA), coaptation distance (CD), tenting area (TA), MV closure angle (MVCA), interpapillary muscle distance (IMD), distance between MV annulus and posterior papillary muscle head (AnAPMD).
Results: Thirty-day and 5-year survival was 91.3% and 82.6%, respectively. 56.5% of patients were operated urgently, 26% needed concomitant MV surgery, patch repair were performed in 47.5%, linear repair in 52.5%. There was a statistically significant increase in LVEF and decrease in LV volumes in the overall population after surgical ventricular repair. Preoperative measured MVAA, CD and TA were significantly higher in 6 patients who needed MV repair/replacement (MVAA 10.7±1.9 vs. 8.8±1,5, p=0.038; CD 12.7±2.9 vs. 10.1±1.6, p=0.026;TA 3.1±±1.6 vs. 1.8±0.4, p=0.020). Postoperative reduction of mitral regurgitation from grade 0.84 to 0.25 in the remaining 17 patients without concomitant mitral

valve surgery corresponded with improvement of MV geometry with significant reduction in ICD, APD, MVAA, TA, CD, MVCA and IMD. We found no clinical or CT-morphological variables of statistical significance that were predictive for decision between linear and patch repair.
Conclusions: Surgical reconstruction of submitral LV aneurysms can be performed with good early and mid-term results. MSCT with possibility to analyze the coherence of ventricular remodeling and geometrical changes in mitral valve apparatus represents an excellent diagnostic tool for pre-operative planning of this complex surgery.

P5401 | BEDSIDE
Profitability of coronary computed tomography as evaluation before valve surgery

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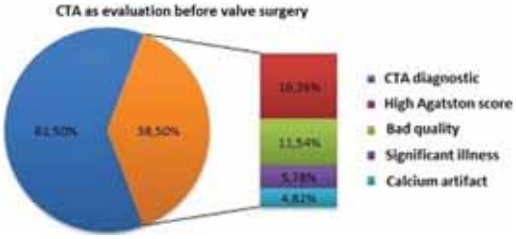
Purpose: The ESC recommends evaluating coronary angiography with IC indication in most patients who are going to valve surgery. Nowadays coronary computed tomography angiography (CTA) is the chosen technique in patients without history of coronary artery disease nor suspected myocardial ischaemia. We analysed the profitability of non-invasive versus invasive coronary angiography (ICA) during a year in a tertiary hospital.
Methods: We analysed all patients with coronary CTA performed between January and December 2011 to evaluate coronary artery disease prior to valve surgery. Multislice CT with 64 detectors was used. When calcium score showed high Agatston score, coronary CTA was not performed and patients were remitted to ICA. If CTA results were not conclusive, or significant lesions were present, they were remitted to cardiac catheterization. Procedure costs were: calcium score 32.26€, coronary CTA 199€ and night at hospital 741.66€. For ICA, one day of hospitalization is needed if no complications appeared. We evaluated profitability of coronary CTA as first choice versus ICA.
Results: 104 patients, whose mean age was 67.2±12.8, were submitted to performed calcium score, and 20 (19.2%) of them were submitted to ICA. 80.8% of patients were scanned, being conclusive in 64 (61.5%) who had no significant coronary illness. Evaluation cost in our centre was 92,177.44€. If all patients had been evaluated only with invasive strategy, the cost would have been 187,476.64€ per year. Therefore costs were reduced by 95,299.2€ in one year.



CTA as evaluation before valve surgery.

Conclusion: Evaluation before valve surgery by multislice CT avoided invasive management in 61.5% of patients and allowed costs to be decreased in 49.2% versus systematic evaluation with ICA, further avoiding complications associated with an invasive strategy.

P5402 | BEDSIDE
Geometrical remodeling of the tricuspid valve in functional tricuspid regurgitation assessed with multi-detector row computed tomography

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Purpose: Multi-detector computed tomography (MDCT) may help to understand the underlying mechanisms of functional tricuspid regurgitation (TR). Present evaluation aimed to assess the geometrical changes of the tricuspid valve in patients with functional TR using MDCT and to correlate these changes with the TR grade.
Methods: In 114 patients (47 men, age 81±8 years), including 33 (28.9%) patients with TR≥3+, the tricuspid valve and right ventricle were geometrically analysed with 320-slice MDCT. The antero-posterior and septal-lateral diameters, perimeter and area of the annulus, degree of tethering of the anterior, septal and posterior tricuspid valve leaflets and right ventricular (RV) volumes and ejection fraction were assessed and subsequently correlated with TR grade in multivariate models. Patients with pacemaker or ICD leads were excluded.
Results: Patients with TR≥3+ had larger tricuspid annulus area (1539.7±260.2 mm^2 vs. 1228.4±243.5 mm^2, p<0.001), larger septal and anterior leaflet angles and larger RV end-systolic volume (93.2±29.8 ml vs. 64.2±23.6 ml, p<0.001) as compared with patients with TR<3+.The antero-posterior tricuspid annulus diameter was independently correlated with TR≥3+, after adjusting for pulmonary hypertension and RV end-systolic volume (Table).

	Multivariate	
	Odds ratio (95% CI)	P-value
Systolic pulmonary artery pressure (mmHg)	1.06 (1.01–1.12)	0.030
Right ventricular end-systolic volume (ml)	1.03 (1.01–1.06)	0.015
Tethering anterior tricuspid leaflet (°)	0.94 (0.79–1.13)	0.522
Tethering septal tricuspid leaflet (°)	1.18 (0.98–1.41)	0.079
Left ventricular ejection fraction (%)	0.95 (0.91–1.00)	0.052
Moderate-severe mitral regurgitation (%)	3.40 (0.88–13.10)	0.075
Baseline model + tricuspid annular anteroposterior diameter (mm)	1.35 (1.07–1.69)	0.010
Baseline model + tricuspid annular septal-lateral diameter (mm)	1.09 (0.94–1.26)	0.254
Baseline model + tricuspid annular perimeter (mm)	1.06 (1.00–1.13)	0.074
Baseline model + tricuspid annular area (mm^2)	1.00 (1.00–1.01)	0.058

Conclusions: In patients with TR≥3+, MDCT demonstrated larger tricuspid annulus and RV dimensions and the antero-posterior annulus diameter was independently correlated with the grade of functional TR.

P5403 | BEDSIDE
Evaluation of valvuloarterial impedance in aortic valve stenosis by cardiac magnetic resonance

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Purpose: In aortic valve stenosis (AVS), valvuloarterial impedance (ZVA), as left ventricle afterload estimation, has been proposed in echocardiography (TEE) to predict adverse outcome better than conventional parameters such as aortic valve area (AVA). However its calculation method differs from standard temporal arterial characteristic impedance (Zc) assessment. The aim of our study was to apply and to validate the Zc concept of measurements to estimate ZVA by using cardiac magnetic resonance (CMR) and carotid tonometry central blood pressure data.
Methods: The study included 40 patients (76±13 years, 21 males) who underwent CMR with carotid tonometry and echocardiography (TTE) the same day. We have evaluated ZVA methods by comparing their links with diastolic dysfunction estimated by E/Ea ratio at TTE.
-ZVA-TTE was the conventional ZVA in TTE: ZVA-TTE=(SAP+MeanGnet)/SVi. SAP is the humeral systolic arterial pressure, SVi the stroke volume index to body surface area, and MeanGnet is the mean gradient taking into account pressure recovery.
-ZVA-MR was formulated as follow: ZVA-MR=(ΔPQ95+MaxGnet)/ΔQ95. ΔPQ95 is the pressure change from the foot to the pressure at the time of 95% of the maximal flow (Q95%). Flow waveform was obtained through LVOT by using phase contrast CMR. Central aortic pressure waveform was obtained by carotid tonometry adjusted by the mean brachial pressure recorded during MR acquisition. MaxGnet is the maximum transvalvular pressure gradient calculated using phase contrast CMR.
Results: ZVA values were higher in symptomatic when compared to asymptomatic patients using both TTE and CMR methods. In univariate analysis, only ZVA when calculated with CMR was correlated with E/Ea (r2=0,25, p=0,001). AVA was also significantly correlated with E/Ea (r2=0.11, p=0,04).
In multivariate analysis to estimate determinants of E/Ea, a significant model including age, mean blood pressure, left ventricular ejection fraction (LVEF), LV mass and aortic valve area was obtained (R2=0,41; p<0,01).However, when ZVA-MR was included, the overall significance of the model was higher (R2=0,56 (p<0,01)). At the opposite to AVA, only ZVA-MR and LV Mass were independently and significantly correlated to E/Ea.
Conclusions: By using CMR in association with central aortic blood pressure, the calculation of ZVA is feasible and can improve left ventricle afterload assessment in AVS. ZVA in magnetic resonance was better correlated with diastolic dysfunction than ZVA estimated by TTE. This new way to estimate ZVA may be clinical useful in evaluation of patient with AVS, especially in asymptomatic patients.

P5404 | BEDSIDE
Multi-center investigations for prevalence of abdominal aortic aneurysm in elderly Japanese patients with hypertension using pocket-sized echocardiography - AAA Japan Study -

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Background: The importance of screening programs for abdominal aortic aneurysm (AAA) is now well recognized, although the ability of physical exam-

ination, as an initial screening tool to diagnose cardiovascular disease, has been declined over the last 20 years. The purpose of this study was to determine the prevalence of AAA in elderly Japanese patients with hypertension and to clarify the diagnostic accuracy of physical examination in the current era, using miniaturized pocket-sized echocardiographic imaging device (pocket-echo).
Methods: This study consisted of 1,731 patients with hypertension aged over 60 years (942 males, mean age 75±8 years) from 20 collaborating institutions. Abdominal palpation was examined on physical examination. The pocket-echo was used for the diagnosis of AAA (defined as greater than 30 mm or more than 1.5 times the diameter of the proximal aorta).
Results: The abdominal aorta was well-visualized in 1,692 (98%) patients. AAA was discovered in 69 (4.1%) patients. Advanced age and male gender were independent risk factors associated with AAA. The incidence of AAA was highest in male aged over 80 (9.2%), whereas lowest in female between 60 and 69 ages (0.6%). Thirty-three AAA was missed on abdominal palpation (sensitivity of 52%). Sensitivity of abdominal palpation increased to 75% in AAA greater than 40 mm.
Conclusions: AAA Japan study was the large multicenter cohort investigation using pocket-echo, to determine prevalence of AAA in Japanese patients with hypertension aged over 60. The results of the present study strongly indicated the importance of AAA screening program in high-risk Japanese population as well as the ability of physical examination to detect large AAA, not for small AAA.

P5405 | BEDSIDE
Association of abnormal aortic wall properties and arterial wave reflections with impaired coronary flow reserve in coronary artery disease patients after successful revascularization

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Impaired coronary flow reserve (CFR) has a prognostic value in CAD patients. Aortic wall properties wall properties and wave reflections determine coronary perfusion, LV function and have and independent prognostic value. We investigated the association of aortic stiffness an abnormal wave reflection with resting coronary flow and coronary flow reserve (CFR) in CAD patients after revascularisation.
Methods: We assessed in 55 patients with CAD and who underwent PCI in LAD or CABG within 6 months. We measured pulse wave velocity using both the Complior (carotid to femoral-PWVc) and Arteriograph apparatus (PWVa-oscillometric method). By means of pulse wave analysis (Arteriograph apparatus) we calculated the central aortic systolic blood pressure (cSBP-mmHg),the return time (RT-ms) and augmentation index (AI) of the arterial wave reflection, the diastolic area (DAI%) of the aortic pulse wave and diastolic reflection area (DRA) an index of diastolic filling of coronary arteries derived by duration of diastole and area between the expected area of the diastolic pressure curve without wave reflection and the true area with reflection. Coronary flow reserve (CFR) of the LAD after adenosine infusion was assessed using Doppler echocardiography. Patients were categorised to those with either normal (>2.5) or impaired (<2.5) CFR.
Results: A decreasing CFR was related with increasing PWVc (r=0.44, p<0.05) PWVa (r=0.45, p<0.05), SBPc (r=0.49, p<0.001), RT, (r=0.45 p<0.01), Aix75 (r=0.50, p<0.01), DAI (r=0.50 p<0.01) and DRA (r=0.55 p<0.001). Additionally a reduced resting coronary flow velocity time integral, a marker of coronary flow was related with reduced DAI% and DRA (r=0.36, r=0.38 p<0.05). Patients with CFR<2.5 had higher PWVc (11.6±2.3 vs. 10.2±1.4, p<0.05) PWVa (10.5±2.3 vs. 9.2±1.4, p<0.05), SBPc (141±20 vs. 123±19, p<0.01), Aix (36±16 vs. 29.2±16, p<0.05) and lower RT (106±21 vs. 123±20, p<0.05), DAI (48±9 vs. 51±6, p<0.05) and DRA (42±8 vs. 51±12, p<0.05). compared with those with CFR>2.5 (p<0.05). By ROC analysis, an PWVa >10 m/sec, SBPc>130 mmHg, RT <120ms, AI <32% and DRA<50 was found to have a sensitivity of 70%,75%,76%, 70%, and 84% and a specificity of 60%, 72%, 67%, 63%, and 64% respectively to identify patients with CFR<2.5.
Conclusions: Abnormal wall properties and wave reflection are related with impaired resting coronary flow and coronary flow reserve after revascularization suggesting a role for pulse wave analysis as a noninvasive test to identify CAD patients with impaired coronary perfusion and thus adverse prognosis despite successful revascularization.

P5406 | BEDSIDE
Aortic root diameters in 1043 healthy subjects

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Purpose: The aim of this study was to explore the full spectrum of aortic root (AR) diameters by two-dimensional transthoracic color-Doppler echocardiography (TTE) in a large cohort of healthy subjects.
Methods: From June 2007 to December 2013, 1043 healthy volunteers [mean age 44.7±15.9 years, range 16 to 92; 503 (48%) men] underwent comprehensive TTE. Two–dimensional measurements of the aortic root were made at end-diastole in parasternal long-axis views at 4 levels: (1) annulus; (2) sinuses of Valsalva; (3) supra-aortic ridge; and (4) proximal ascending aorta.
Results: The absolute aortic diameters were significantly greater in men than in women at all levels while BSA indexed aortic diameters were greater in women. (Table 1) There was a straight correlation between the aortic diameters (absolute and indexed values) with age in both genders (p=0.0001).

Table 1. Gender differences in aortic diameters

Aortic Root		Absolute Values (mm)			Indexed Values (mm/m^2)		
		Men	Women	p	Men	Women	p
Annulus	mean	21.0±2.2	18.7±1.6	0.0001	10.9±1.3	11.2±1.1	0.0001
	25th	19.2	18.0	10.0	10.5		
	75th	22.0	20.0	11.7	11.9		
Sinuses of Valsalva	mean	31.8±3.7	28.5±3.0	0.0001	16.5±2.2	17.1±2.1	0.0001
	25th	29.0	26.0	15.1	15.7		
	75th	34.0	31.0	17.8	18.3		
Sinotubular junction	mean	26.9±3.7	24.4±2.9	0.0001	14.0±2.1	14.6±1.9	0.0001
	25th	24.0	22.0	12.5	13.4		
	75th	29.0	26.0	15.2	15.8		
Proximal acending aorta	mean	29.1±4.3	27.4±3.4	0.0001	15.1±2.5	16.5±2.1	0.0001
	25th	26.0	25.0	13.5	15.1		
	75th	32.0	30.0	16.6	17.8		

Data are presented as mean ± standard deviation, 25 and 75 percentile. p values indicate the differences among genders.

Conclusions: We provide the full range of AR diameters by TTE. Knowledge of upper physiologic limits of aortic dimensions is mandatory in order to detect aorta dilatation and planning appropriate follow-up and therapeutic interventions.

P5407 | BEDSIDE
Atherosclerotic disease of the thoracic aorta, carotid intima-media thickness and plaque as predictor of cardiovascular mortality and cerebrovascular and coronary events

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Objective: To evaluate the severity and extent of thoracic aortic plaques, carotid intima-media thickness and plaque and its relationship with mortality and cerebrovascular and coronary events.
Material and methods: Between 2005 and 2007, 542 patients (ps) were referred for evaluation with transesophageal echocardiography (TEE). Age: 65.08±13.32 years. Male gender: 306 patients (ps) (56.5%). The following variables were included: reason for ordering the study (embolic source 37.5%, endocarditis 22.5%, previous to cardioversion 10.9%, mitral valve disease 10.1%, other reasons 19.4%), risk factors (diabetes, smoking habits, hypertension, dyslipidemia) and presence of atrial fibrillation. Common carotid intima-media thickness (IMT) was manually measured or the presence of carotid plaques was registered. According to aortic findings the patients were divided into two groups: a-with uncomplicated aortic plaques <4 mm: ps= 413 and b-with complex aortic atheromatosis (CAA): aortic plaques ≥4 mm, with ulcers, thrombi or aortic debris: ps = 129. Follow-up: 1596 days (mean: 759 days). A total of 474 ps (87.45%) were contacted; the following events were considered: transient ischemic attack or stroke, AMI, angina, revascularization and/or cause of mortality during that period. Multivariate analysis was used to identify independent predictors. A p value <0.01 was considered statistically significant.
Results: Global mortality during follow-up was 13.3% (n=63). Cardiovascular mortality was 3.6% (13/365) in the group of patients with simple or uncomplicated plaques or with absence of plaques and 17.4% (19/109) in the group with CAA (p<0.01). There were 132 combined cerebrovascular and/or coronary events; 89 in the group without CAA (89/365; 24.4%) and 43 in the group with CAA (43/109; 39.4%) (p<0.01). These differences were significant at multivariate analysis (OR 3.79, 95% CI 1.72-8.30 p=0.0009 and OR 1.89, 95% CI 1.15-3.09 p=0.01 respectively). Cardiovascular mortality was 2.7% (7/255) in pts without carotid plaques and 11.4% (25/219) in pts with carotid plaques. These differences had a weak statistic significant at multivariate analysis (OR 2.83, 95% CI 1.14-7.01 p=0.025). There were no significant differences in IMT between patients with and without events
Conclusions: In this population, CAA was an independent predictor of cardiovascular mortality and combined vascular events and the presence of carotid plaques was an independent predictor of cardiovascular mortality. IMT was not an independent predictor of cardiovascular mortality or combined vascular events.

INNOVATION IN IMAGING

P5409 | BENCH
Echocardiography combined to spatiotemporal image correlation in the prenatal diagnosis of total anomalous pulmonary venous connection

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Objective: Prenatal diagnosis of total anomalous pulmonary venous connection

(TAPVC) is challenging even for experts. We sought to explore whether the use of spatiotemporal image correlation (STIC) can supply additional information with respect to conventional fetal echocardiography in the prenatal diagnosis of TAPVC.
Methods: Twenty-two cases diagnosed as TAPVC received fetal echocardiography examination from April 2009 to December 2013. Four-dimensional volumes from 16 cases of suspected TAPVC by conventional echocardiography at our hospital. Echocardiographic characteristics were compared with the results of postnatal work-up and pathology.
Results: Prenatal diagnosis was made at a mean gestational age of 26.6 (range 21 to 36) weeks. TAPVC was found in 22 cases by fetal echocardiography; four cases were isolated TAPVC, eighteen TAPVC had associated cardiac anomalies. Among them, nine cases were supracardiac types, five cases were infracardiac types and eight cases were intracardiac types. Twelve true positive cases of TAPVC were confirmed after birth or pathology. The fetal echocardiographic characteristics of 22 fetuses with TAPVC included absent insertions of pulmonary veins in the LA, increased distance between left atrium (LA) and descending aorta, presence of a confluence behind the left atrium, increased angle between left and right pulmonary veins. 4D ultrasound with STIC clearly visualized the anomalous PV confluence and/or the draining vertical vein in all sixteen cases examined.
Conclusion: There are fetal echocardiographic characteristics of TAPVC. Conventional fetal echocardiography plays an important role in prenatal diagnosis of TAPVC. 4D ultrasound with STIC should be proposed to identify abnormal venous drainage at the screening level, thus supplying additional information over that provided by 2D fetal echocardiography.

P5410 | BENCH
Acoustically active catheter prototype: selective detection of its tip by Doppler ultrasonography

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Purpose: To develop an ultrasound-based catheter navigation system that does not rely solely on catheter tip identification by artifact-prone B-mode (grayscale) echocardiographic scans; instead, the catheter tip is unambiguously detected by a novel use of Doppler ultrasound.
Methods: A 2-mm piezoelectric crystal was affixed at the tip of a catheter prototype and connected to a waveform generator. We hypothesized that crystal vibrations of appropriate frequency and amplitude will interact with an incoming Doppler ultrasound signal and produce a new signal interpreted as a unique Doppler shift. If this hypothesis was correct, then a color spot would be generated and mark the location of the catheter tip in color flow Doppler (CFD) images. We used an elastic mechanical model of a beating left ventricle (LV) with stroke rate and volume set to 70 beats/min and 70 ml, respectively.
Results: We found that driving the crystal by a sinus signal of 1-3 kHz frequency at 10-20 Volts produces interactions interpreted by a clinical echo machine as a Doppler shift within 0.4-1.2 m/s range and depicted in the CFD mode as a color "halo" around the vibrating crystal inside the LV model (Fig. 1A). The "halo" can be masked by colors of intraventricular flow, but pulsed-wave Doppler (PWD) can be used to display the crystal-generated Doppler shift by the velocity graph (Fig. 1B). By adjusting the CFD scale, colors depicting intraventricular flow are minimized and the catheter tip becomes clearly color-marked (Fig. 1C).

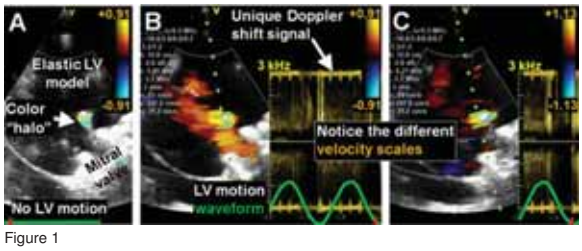

Figure 1

Conclusions: We have developed an initial prototype of an acoustically active catheter whose tip can be uniquely color-marked within CFD images. Animal studies are required to preclinically test this novel use of Doppler imaging for catheter tip detection and navigation inside a life heart.

P5411 | BEDSIDE
Role of 18F-FDG PET/CT in the diagnosis of infective endocarditis in patients with implanted cardiac devices: a prospective study

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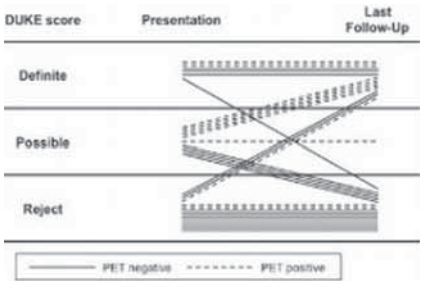
Purpose: The diagnosis of IE is currently based on the modified DUKE criteria, where the only validated imaging technique is echocardiography and remains challenging. The aim of the study was to assess the diagnostic role of 18F-fluorodeoxyglucose positron emission tomography/computerized tomography (PET/CT) in patients with implanted cardiac devices and suspected IE.
Methods: We prospectively analysed 27 patients evaluated for suspected device-related IE between January 2011 and June 2013. The probability of IE was defined at presentation according to the modified DUKE criteria and PET/CT was performed as soon as possible. Patients underwent medical or surgical treatment based on the overall clinical evaluation. During follow up, we considered: lead cultures in patients who underwent extraction, direct inspection and lead cultures in those who underwent surgery and a clinical/instrumental re-evaluation after at least 6 months in patients who received antimicrobial treatment or had an alternative diagnosis and were not treated for IE. After the follow up period, diagnosis was reviewed by the multidisciplinary team, using the modified DUKE criteria and considering the new findings.
Results: Among the 10 patients with positive PET/CT, 7 received a final diagnosis of "definite IE", one of "possible IE" and two of "reject IE". Among the 17 patients with a negative PET/CT, 4 were false negatives and received a final diagnosis of "definite IE". These patients underwent PET/CT after having started antibiotic therapy or had a technically suboptimal exam.



Results of PET/CT and Duke score

Conclusions: In patients with cardiac devices, PET/CT increases the diagnostic accuracy of the modified Duke criteria, particularly in the subset of patients with "possible IE" in whom it may help the clinician to manage a challenging situation.

P5412 | BEDSIDE
Incremental value of pocket-sized hand-held echocardiography in bedside outpatients cardiology consultations, in addition to physical examination: a multicentric italian study (SIEC)

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Purpose: Pocket Hand-Held Echocardiography (PHHE) has recently been introduced and can potentially improve the diagnostic accuracy of clinical examination. The aim of the study was to assess the incremental value of PHHE system in initial outpatient cardiology consultations, in addition to physical examination integrated by ECG and chest-X-ray.
Methods: 443 patients (53% men), referred for cardiology consultations, were studied in 5 Centers in Italy. Each patient underwent to physical examination, with ECG and Chest-X-Ray, followed by PHHE (VScan, GE Healthcare)assessment. Scanning time, the number of examinations with abnormal results after physical examination and the PHHE, and the information obtained by physical examination alone and followed by the PHHE were assessed.
Results: The main consultation motives were: dyspnea (29.3%), chest pain (24%), arrhythmias (19%), shock (2.3%), syncope (6.1%), before surgery cardiologic evaluation (24.4%). The scanning time with the PHHE was 184±83 seconds. The main diagnoses made with PHHE were: increase of left and or right ventricular volume, atrial dilation, left ventricular hypertrophy or dilation, myocardial infarction (ACS), global LV dysfunction, mitral or aortic valvular insufficiency or stenosis, pericardial effusion.
If we analyze the correspondence between the diagnosis obtained by clinical examination, with the aid of ECG and chest X-ray and the PHHE results, it should be noted that only 26% execution of PHHE has had no influence on the final diagnosis, while in 24% the diagnosis obtained through the clinical approach was however confirmed and verified by PHHE. Instead, it appears very important to note that in 24% of the clinical diagnosis was enriched and better defined by PHHE and in 26% the diagnosis was even changed. One can therefore affirm that in our study population in almost 50% of cases PHHE allowed a diagnosis certainly more complete and in about half of these cases even led to a net change of diagnostic orientation.
Conclusions: The PHHE utilization does not significantly increase the duration of consultations. It showed an incremental value over physical examination (increased number of corrected diagnoses), reducing the use of routine echocar-

diography, increasing the number of adequate echocardiographic studies and determining a large number of releases from the outpatient clinic. This ultrasonic approach has a significant impact on the decision making of the patient, allowing an accurate and rapid diagnosis and a better stratification of patients.

P5413 | BEDSIDE
Right heart in young people by three-dimensional (3D) and Speckle Tracking echocardiography: atrial and ventricular volumes and deformation properties study

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Background: RV (right ventricle) plays an important role in determining cardiac symptoms in several diseases and RA (right atrium) is a quantitative marker of RV dysfunction severity. Real-time 3D echocardiography (3DE) enables accurate ventricle and atrial volume measurement. Speckle Tracking is a sensitive tool to quantitatively assess regional deformation properties.
Purpose: To obtain normal reference ranges for RA volumes, RA EF, by 3D (both software Auto LVQ GE Heathcare and TomTec 4D), RV volumes, RV EF, by 3DE (TomTec) and RA and RV deformation properties by Speckle Tracking and intra and inter-observer reproducibility.
Methods: 70 subjects, 38 males and 32 females, aged 25±7 yrs, without any cardiovascular disease, were included. By E9GE we measured RA (maximum and minimum) both by biplane method and by 3D and 4D methods, and RV volumes (in apical 4-chamber, short-axis, and coronal views) by tracing endocardial borders at ventricular end-systole and end-diastole. Volumes were indexed for body surface. By Speckle tracking we measured 2D longitudinal systolic RA and RV Strain (S) and Strain rate (SR) in apical 4-chambers view, at level of RA and RV free wall (basal, medium and apical segments).
Results: We have reported, in young people, references range of RA and RV volumes: 2DRA maximum 32,35±8,2 ml, indexed 18,27±4,14 ml/mq, minimum 15,46±4,12 ml, indexed 8,7±1,9ml/mq; 4DRA maximum 43,09±11,21 ml; indexed 24,25±5,25 ml/mq; minimum 22,32±6,14 ml; indexed 12,54±2,86 ml/mq; 3D TomTec 41,68±12,22 ml, indexed 23,35±5,69 ml/mq; minimum 23,3±7,9ml, indexed 13,08±3,7 ml/mq; 3D RV end-diastolic:33±11ml/mq; end-systolic volume:16±6ml/mq; and RA and RV ejection fraction: 2D RAEF 52±7,5%; 4D RAEF 47,8±7,35%; 3D RAEF 44,36±7,63%; 3D RVEF 67±8%. We found a gradient between different segments for RA S (basal>80%, medium 62,51±9,66%, apical 26,54±3,56%); RA SR (basal 5,1±0,71S-1; medium 3,33±0,61S-1; apical 2,1±0,26S-1); RV S (apical -24,59±4,8%; medium -29,69±4,78%; basal -30,1±5,88%); RV SR (apical -1,44±0,25 S-1, medium: -1,78±0,37 S-1, basal:-2±0,4 S-1). For RA volumes we found significant differences only between 2DE and 3DE methods (p<0,0001) and not between the two 3D methods (p=0,6). Inter and intraobserver variability coefficients were 7% and 4% for 3D volumes and 8% and 4% for S-SR measurements, respectively.
Conclusions: The present study provides normal reference values for RA and RV volumes and EF by 3DE and normal longitudinal RA and RV deformation values in young people. 3DE overcomes the limitations of 2DE to assess the complex anatomy of the RV and 2DE underestimation of RA volumes.

P5414 | BEDSIDE
Which are the optimal settings of 3D datasets used for left ventricular quantitative analysis by three-dimensional speckle-tracking echocardiography?

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Purpose: To identify the optimal trade-off between temporal (TR) and spatial resolution (SR) for LV quantitation by three-dimensional speckle-tracking (3DSTE).
Methods: Twenty-two consecutive patients (pts, 16-81 years, LVEF 18-74%) underwent CMR and echo <24h apart. LV 3D datasets were obtained with Vivid E9 (GE Vingmed, N) using 9 different combinations of stitched cycles (2-/4-/6-beat) and SRs (line density, L1>L2>L3). LVEDV, LVEF, global longitudinal (3DLε) and area strain (3DAε) were analyzed using automatic algorithm (BT13) and compared against CMR, 2DLε (at 72±8 fps) and 3DSTE analysis by expert (3Dex).
Results: Smallest LVEDV bias versus CMR was achieved at 6-beat (33±17 ml vs 39±20 ml at 2-beat, p<0.01). No change in LVEF was seen when cycle number was increased (bias 3±5% at 2-beat vs 2±6% at 6-beat, p=NS). Reducing SR resulted in larger underestimation of LVEDV (bias vs CMR: 33±17 ml at L1 vs 43±20 ml at L3, p<0.01) and in LVEF change from 3% bias at TR 15-30 vps to -2% bias at TR>55 vps. Six-beat datasets provided the closest correlation of 3DLε with 2DLε (Table), and of 3DAε with LVEF (r 0.85). TR optimization by reducing SR worsened the agreement between 3DLε and 2DLε (Table). 3Dex (LVEDV r 0.93, bias 24±14ml; LVEF r 0.95, bias 1±4%) was more accurate than all automatic analyses (p<0.01).
Conclusions: Six-beat datasets with highest SR and TR between 35-55 vps provided the best overall accuracy for LV quantitation by automated 3DSTE analysis. The addition of manual editing and tracking optimization by expert further improved 3DSTE accuracy.

	Setting	TR (vps)	R Pearson	Bias±SD (%)
3DLε	2-beat/L1	15±2	0.74	3.9±3.7
	2-beat/L2	19±2	0.72	4.4±4.0
	2-beat/L3	31±4	0.55	7.1±4.8
	4-beat/L1	29±5	0.77	4.6±3.6
	4-beat/L2	37±6	0.82	5.8±3.7
	4-beat/L3	64±8	0.78	7.7±4.1
	6-beat/L1	44±6	0.81	5.8±3.4
	6-beat/L2	57±6	0.83	6.6±3.8
	6-beat/L3	89±8	0.86	7.3±3.8
$3D_{ex}$ Lε	6-beat/L1	44±6	0.86	3.7±2.9

P5415 | BEDSIDE
Gender difference of cardiovascular morphological characteristics of patients with ellipsoid-shaped aortic annulus evaluated by three-dimensional transthoracic echocardiography

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Background: Three-dimensional (3D) transthoracic echocardiography (TTE) has developed and provided a detailed shape of aortic annulus, and then we previously reported that an angle between interventricular septum and ascending aorta (IVS-Ao angle) was independently associated with a morphological change of aortic annulus in patients without cardiovascular disease. The purpose of our present study is to investigate the gender difference of parameters associated with the morphological change of aortic annulus.
Methods: Two-dimensional and 3D TTE was performed in 108 patients without cardiovascular disease (age: 56±18 years, 53 males). Using the cutting image obtained by 3DTTE, we measured the minimum and maximum diameters of aortic annulus, the diameter of Valsalva sinus (Val) and the IVS-Ao angle, and then the eccentricity index of aortic annulus (EI: 1 – minimum diameter/maximum diameter) was calculated and the Val was indexed by the body surface area. Between male and female patients, we compared the relationships between EI and age, body mass index (BMI) or echocardiographic indexes.
Results: IVS-Ao angle, age and Val index were correlated with EI in both male and female patients (Table). On multivariate regression analysis by these parameters, in male patients, IVS-Ao angle and Val index were independently associated with EI (β= -0.52; p<0.01, β= 0.32; p<0.01, respectively). On the other hands, in female patients, only IVS-Ao angle had independent association with EI (β= -0.50; p<0.01).

	Male (n=53)		Femal (n=55)	
	r	p	r	p
IVS-Ao angle	-0.60	<0.001	-0.69	<0.001
Age	0.59	<0.001	0.63	<0.001
Val index	0.45	<0.001	0.48	<0.001

Conclusions: Our findings suggest that acute angle between the interventricular septum and the ascending aorta is involved in the ellipsoid-shaped aortic annulus regardless of the gender. In addition, in male patients, dilatation of Valsalva sinus may also leads to ellipsoid-shaped aortic annulus.

P5416 | BENCH
Using volume rendered CT images in teaching anatomy to medical students

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Purpose: There is still a big debate on the pros and cons of theoretical and practical teaching methods. Evolution of the multi-detector computed tomography technology has allowed for high resolution imaging and 3D reconstruction of the heart. The objective of this study was to assess if the anatomy of the heart could be taught to first year medical students using volume rendered CT images. Furthermore, we sought to investigate the effectiveness of this practical teaching method compared to theoretical oral lecture and practical dissection practice.
Methods and materials: 73 first year medical students who achieved at least 80% on their first midterm exam took part in the study. Students were randomized into three groups: theoretical lecture (TL, n=22), practical dissection (PD, n=27) and practical radiology (PR, n=24) group. All groups took part in a 2 hour course focusing on the macroscopic features of the heart. The effectiveness of the teaching techniques was tested by a written exam five days after the classes. The exam consisted of 25 theoretical questions and a practical part where 25 features had to be identified on anatomical specimens. Since motivation and other psychological aspects contribute to the effectiveness of a teaching method, a 5 point opinion questionnaire was filled out by the students before and after the exam. Kruskal-Wallis ANOVA test was used to compare the three groups.
Results: The PD and the PR group scored significantly higher on the practical questions and on all opinion questionnaire scores compared to the TL group (median score: 9, 6, 5.5, respectively, p<0.05). No significant differences were seen

in the theoretical question scores between the three groups. (median score: 17, 18, 16, respectively, p=0.22).
Conclusions: The results show that practical teaching methods seem to be more effective in teaching anatomy compared to theoretical teaching methods, and suggest that modern radiological approaches can be of additive value in teaching anatomy.

P5417 | BEDSIDE
Neural network model for prediction and prognosis of myocardial infarction in patients with previous revascularization; 15-year experience

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The purpose of this study was to assess the usefulness and accuracy of artificial neural network in the prediction and prognosis of acute myocardial infarction (AMI) in patients with previous coronary artery bypass grafting (CABG).
Materials and results: From January 1999 to January 2014, the baseline characteristics and clinical data were recorded in 4360 consecutive patients. The data set contains 13 predictor variables per patient. It was first randomly split into training (2180 cases) and test sets (2180 cases). Artificial neural network performance was evaluated using the original data set for each network, as well as its complementary test data set, containing patient data not used for training the network. The program compared actual with predict outcome for each patient, generating a file of comparative results. At the end, results from this file were analyzed and compared, on the basis of receiver operating characteristics (ROC) areas. Logistic regression analysis, as one of standard prediction model, was not efficient for prediction and prognosis of acute myocardial infarction in patients with prior CABG. The results show that a traditional statistical model is not able to perform class separation in multidimensional space and that a nonlinear approach is justified. In analyzing the performance of neural network in outcome prognosis of AMI in patients with previous CABG it is clear that neural network method was better for almost all statistic parameters for all analyzed prediction variables.
Conclusions: In this clinical situation, artificial intelligence appears to be superior to traditional method for prediction and prognosis of AMI in patients with previous CABG.

P5418 | SPOTLIGHT
Learning cardiovascular pathophysiology by creating your own virtual patient with CircAdapt simulator

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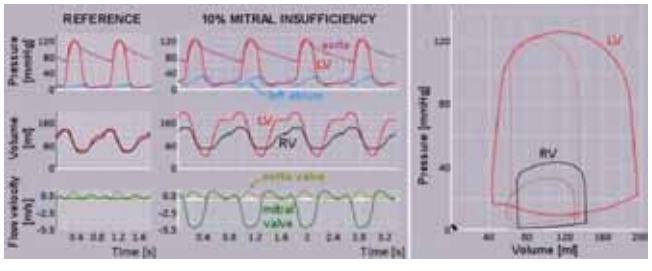
Purpose: To develop a user-friendly interactive simulation environment that can be used by medical students and clinical fellows with the aim to improve their understanding of cardiovascular hemodynamics and related physiology and pathophysiology.
Methods and results: The CircAdapt model of the human heart and circulation forms the core of the CircAdapt Simulator freeware. Valves, large blood vessels, atrial and ventricular cavities, myocardial tissue and peripheral resistances are represented by modules each incorporating established physiological and physical principles. These modules form a network, representing the entire cardiovascular system. It enables real-time simulation of dynamic pressure, volume and blood flow velocity tracings in the heart, blood vessels, valves and shunts, if present. The CircAdapt Simulator is designed as an interactive user-friendly shell around the CircAdapt model. Without much foreknowledge, a novice user can intuitively simulate complex pathophysiological situations by manipulating for instance diameter and leakage of heart valves (figure), contractility and stiffness of cardiac walls, stiffness of arteries, and by the creation of shunts. A wide selection of haemodynamic signals can be displayed as required to show resulting effects. Presently, the CircAdapt Simulator is successfully integrated into the first, second and third year of our institute's medical school.



Conclusions: The CircAdapt Simulator is an innovative freeware tool for teaching cardiovascular physiology and pathophysiology over a wide range of disciplines. It is an excellent tool for education of medical students and for analyzing more complex clinical cases by trainees in different disciplines such as cardiology, neonatology, pulmonology and critical care medicine.

EARLY AND LONG-TERM OUTCOME OF PCI

P5420 | BEDSIDE
Long-term clinical outcome after coronary revascularization in hemodialysis patients

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Background: Although coronary revascularization, regardless of surgical or percutaneous procedures, has been widely performed in hemodialysis (HD) patients, the long-term outcomes remain unknown in such population who are at the highest cardiovascular risk. We investigated clinical outcome after various coronary revascularization in HD patients.
Methods: A total 997 maintenance HD patients electively undergoing coronary revascularization were enrolled. Patients were divided into 4 groups; patients underwent coronary artery bypass grafting (CABG group, n=210), drug-eluting stenting (DES group, n=345), bare metal stenting (BMS group, n=273) and angioplasty alone (POBA group, n=169). They were followed up to 7-year, and the incidence of major adverse cardiac events (MACE) as a composite endpoint including all-cause death, non-fatal myocardial infarction (MI) and target lesion revascularization (TLR) were analyzed.
Results: Prevalence of diabetes, multi-vessel disease, left main trunk lesion and left ventricular ejection fraction <40% were higher in CABG group than other groups. During follow-up period (median: 39 months), 453 MACEs (death: 304, MI: 43 and TLR: 271) occurred.
7-year event-free survival rates for MACE and TLR were 57.1%, 53.4%, 36.4% and 29.8%, and 86.0%, 71.6%, 54.2% and 41.2% in CABG, DES, BMS and POBA groups, respectively ($p<0.0001$ in both). On Cox multivariate analysis, CABG group had advantage for TLR compared to all other groups (adjusted HR 0.38, 95%CI 0.22-0.62, $p<0.0001$ vs. DES group, adjusted HR 0.23, 95%CI 0.14-0.37, $p<0.0001$ vs. BMS group and adjusted HR 0.16, 95%CI 0.09-0.27, $p<0.0001$ vs. POBA group, respectively), however, had no advantage for MACE compared to only DES group (adjusted HR 0.86, 95%CI 0.64-1.15, p=0.33 vs. DES group, adjusted HR 0.58, 95%CI 0.44-0.77, p=0.0002 vs. BMS group and adjusted HR 0.49, 95%CI 0.36-0.65, $p<0.0001$ vs. POBA group, respectively). All-cause survival rates were comparable among groups (65.0%, 67.7%, 55.9% and 53.4% in CABG, DES, BMS and POBA group, respectively, p=0.067).
Conclusion: CABG might have totally clinical advantage compared to other procedures even though the survival rate was comparable in HD patients. However, this advantage may be potentially reduced in the refined DES era.

P5421 | BEDSIDE
Cabg clinical syntax score and euroscore as predictors of long term clinical outcomes in patients with previous coronary artery bypass grafting undergoing percutaneous coronary intervention

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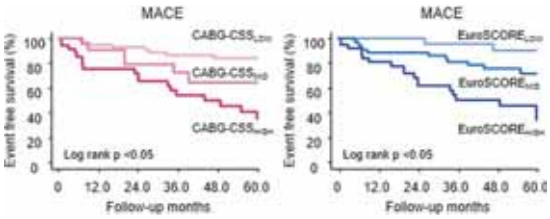
Purpose: SYNTAX Score based on lesion-based scoring system was developed among previous CABG patients (CABG SYNTAX Score). The Clinical SYNTAX Score (CSS), combining the SYNTAX Score with a simple clinical risk score, has established itself as an important prognostic tool in patients undergoing percutaneous coronary intervention (PCI). However, few data exist regarding scoring system for predicting long-term outcome in patients with previous CABG undergoing PCI. Therefore, the aim of this study was to assess whether the CSS in patients with previous CABG undergoing PCI (CABG-CSS) would predict long-term outcome after PCI.
Methods: Between April 2005 and March 2012, 129 patients previous CABG with successful drug eluting stent implantation were retrospectively analyzed. The CABG-CSS was calculated by multiplying the CABG SYNTAX Score to (age/left ventricular ejection fraction +1 for each 10mL the estimated glomerular filtration rate <60 ml/min per 1.73m^2). Major adverse cardiac events (MACE) were defined as the occurrence of cardiac death, myocardial infarction and target lesion revascularization (TLR).
Results: Median interval from CABG to PCI was 5 years. Native coronary artery accounted for nearly all of target (native coronary PCI; n=118). During follow up, the overall cardiac death, myocardial infarction, and TLR were occurred in 7.0, 1.6 and 15.5%, respectively. In multivariate analysis, CABG-CSS and EuroSCORE were identified as predictor of MACE, but the CABG SYNTAX score was not. Stratifying outcomes across CABG-CSS and EuroSCORE tertiles showed similar results for the comparisons between high and low score tertiles (Figure).



MACE-free survival stratified by score.

Conclusion: Measurement of the CABG-CSS and EuroSCORE could provide an important insight to predict long outcome among previous CABG patients undergoing PCI.

P5422 | BEDSIDE
Effects on left ventricular function of Impella-assisted PCI in high risk patients

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Background: Poor left ventricular (LV) function and multivessel disease with an extensive amount of LV at risk during the procedure are known risk factors for adverse outcome in patients undergoing percutaneous coronary interventions (PCI). Impella Recover LP 2.5 provides percutaneous LV unloading and may help LV tolerate ischemia related with PCI. No study assessed the impact of PCI with IMP assistance on LV function.
Methods: Patients with poor LV function and multi-vessel or left main coronary artery disease were considered at high risk and underwent PCI with the pre-intervention IMP implantation. The device was planned to be removed after PCI unless haemodynamic instability was present. LV ejection fraction (EF) was assessed by echocardiography before procedure and at follow-up (after >6 months).
Results: A total of 45 patients (age 72±11, 94% males) underwent high-risk PCI at our Centre with IMP assistance. Pre-PCI LVEF was 32±8%. IMP was implanted before PCI by femoral approach and PCI was performed by radial approach or by contralateral femoral approach. After PCI, IMP was removed in all patients, and insertion-site haemostasis was obtained by pre-implanted double Perclose suture device. After a follow-up duration of 16±9 months 40 patients (89%) were alive. At follow-up echocardiography, LVEF showed a significant improvement (LVEF: 38±9%; P<0.001 vs pre-PCI). Of note, 57% of patients had an increase ≥5% of LVEF at follow-up.
Conclusions: IMP-assisted PCI in high risk patients is feasible and may improve left ventricular function.

P5423 | SPOTLIGHT
Cause and time of death associations in patients treated with percutaneous coronary intervention for non ST-elevation myocardial infarction

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Associations between time and cause of death in a large consecutive cohort of patients with non ST-elevation myocardial infarction (NSTEMI) remain unclear.
Methods: This is an observational cohort study of consecutive NSTEMI patients treated with percutaneous coronary intervention (PCI) in Eastern Denmark. Data were obtained from the Eastern Danish Heart Registry, Danish Centralized Civil Registration system and Cause of Death Registry.
Results: From 2003–2012 percutaneous coronary intervention (PCI) was performed on 5,864 consecutive NSTEMI patients (mean age 65.9±12.1 years, 71.9% men). During 22,159 patient-years of follow-up 1080 patients died. 30-day, one year and 5-year cardiac mortality rates were 1.2%, 4.0% and 8.7%, respectively. The corresponding 30-day, 1-year and 5-year all-cause mortality rates were 1.5%, 6.0% and 14.8%, respectively. Causes of death were cardiovascular in 54.2% (n=585) and non-cardiovascular in 45.8% (n=495) of cases during the whole study period. Cardiovascular death (83.7%) was the main cause of mortality during the first thirty days. 55.8% of 30-day-mortality was due to acute myocardial infarction and 7% due to cerebral infarction and bleeding. After thirty days and up to 1 year cardiovascular death was responsible for 60.5% of mortality. After 1 year and onwards non-cardiovascular deaths were responsible for 51.6% of mortality, with cancer attributing to 22.4% of the total mortality. After 5 years non-cardiovascular death was the leading cause of mortality (65%).
Conclusions: Cardiac deaths after PCI occur mainly in the first month and remain the leading cause of mortality during the first year. Non-cardiac causes are responsible for the majority of deaths after 5 years.

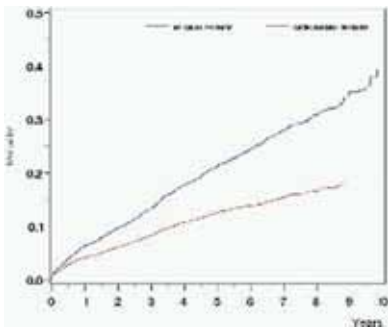
Figure 1. Mortality in NSTEMI.

P5424 | BEDSIDE
Long-term prognostic impact of in-hospital cerebrovascular accidents and stent thrombosis in patients undergoing percutaneous coronary intervention

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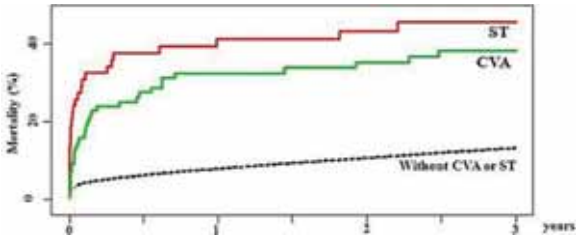
Introduction: In-hospital cerebrovascular accidents (CVA) and stent thrombosis (ST) are rare but serious adverse events after percutaneous coronary intervention (PCI). CVA and ST after PCI are associated with a poor outcome but their relative contribution to long-term mortality has not sufficiently been investigated.
Methods: The study included 18 334 consecutive patients who underwent PCI. The CVA and definite ST were diagnosed according to the accepted criteria. Patients were divided into 3 groups: the group with CVA, the group with ST and the group with none of these events. The primary outcome was all-cause mortality. The length of follow-up was 3 years.
Results: In-hospital CVA was observed in 90 patients (0.49%) and ST in 59 patients (0.32%). The majority of CVAs (87.8%) were of ischemic origin. Multivariate logistic regression analysis showed that sex female, presentation with an acute coronary syndrome and lower ejection fraction were independently associated with an increased risk of in-hospital CVA, whereas the use of bare-metal stents or first generation DES (compared with second generation DES), multivessel disease, post-PCI residual stenosis and presentation with an acute coronary syndrome were independently associated with an increased risk of in-hospital ST. The Kaplan-Meier estimates of 3-year mortality were 35.6% (32 patients) in the group with CVA, 44.1% (26 patients) in the group with ST and 11.5% (2091 patients) in the group without CVA or ST (log-rank test P<0.001). There was no significant difference in the 3-year mortality between CVA and ST groups (P=0.30).



Mortality at 3 years in the three groups.

Conclusion: The in-hospital occurrence of CVA or ST after PCI is rare but associated with a poor long-term prognosis. Both events seem to have a similar impact on long-term survival.

P5425 | BEDSIDE
Survival after percutaneous coronary intervention (PCI): comparison of patients with or without left anterior descending stenosis in elective PCI for left main disease and triple vessel disease

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Background: Patients with significant left anterior descending artery disease, particularly when the proximal segment is involved (termed pLAD), are considered to have an adverse cardiac prognosis compared with patients with coronary artery disease but absence of pLAD.
Objective: We aimed to find out if the long term mortality of patients with pLAD among a cohort with three vessel diseases (TVD) and/or left main stenosis (LMS) was higher than that without pLAD.
Methods: Patients undergoing elective PCI with drug eluting stents (DES) for LMS or TVD were included in this cohort study. Important exclusion criteria were previous coronary artery bypass surgery, high-risk acute coronary syndrome including myocardial infarction. All-cause death was the primary endpoint; survival was assessed by systematic patient contacts after 30 days, at one, two and three years. In all patients, we calculated SYNTAX score and logistic EuroScore. We

used the Kaplan-Meier method to estimate the mortality and calculated adjusted hazard ratios by Cox models.
Results: We identified 1,262 patients who met the entry criteria, thereof 24% female. Mean age was 67.7±10.3 years. Median follow up (interquartile range) was 1120 (985 – 1391) days. Mean SYNTAX score was 21.3±8.6. pLAD was present in 364 patients (28.8%). SYNTAX score in group with pLAD was higher (20±8.4 vs. 24.7±8.2, $p<0.01$) than that without pLAD. There was no significant difference of one-year, two-year and three-year mortality between both groups (3±0.9% vs. 2.9±0.6%; 5.0±1.2% vs. 5.2±0.7; 8.0±1.5% vs. 8.2±1.0%, p=0.67; 0.64; 0.69). In the cohort without LMS, one-, two- and three-year mortality between the group with and without pLAD showed also no significant difference (2.1±0.8% vs. 2.7±0.6%; 4.5±1.2% vs. 5±0.8; 7±1.6% vs. 7.2±0.9%, p=0.26; 0.38; 0.62).
Compared to the group without pLAD, the hazard ratio (95%-confidence interval) for mortality in the pLAD group was 1.08 (0.76–1.54, p=0.67). Even after adjustment for SYNTAX score and logistic EuroScore, pLAD was not predictive for mortality (adjusted hazard ratio 1.34 (0.94–1.94), p=0.11). In contrast, SYNTAX score and logistic EuroScore were highly predictive, with hazard ratios (per unit) of 1.05 (1.03–1.07) for SYNTAX score and 1.08 (1.06–1.09) for logistic EuroScore ($p<0.001$ for both variables).
Conclusion: Complexity of coronary artery disease determined with SYNTAX score and clinical risk profile determined with logistic EuroScore are strong predictors of three year survival after elective PCI with DES. In contrast, pLAD as single criterion showed no significant prognostic relevance.

P5426 | BEDSIDE
Are PCI with long stent lengths safe in the DES era?

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Background: Long stent lengths have been shown to be predictive of cardiovascular (CV) events and stent thrombosis after percutaneous coronary intervention (PCI), whether it remains true in the DES era remains unclear.
Purpose: To compare one-year outcomes after PCI according to total length of stent in the DES era.
Methods: Consecutive patients referred to our Cath-Lab for PCI were included within 52 months. Clinical and angiographic data were prospectively entered into the nationwide web-based "Middle-Care" database, one year follow up was obtained by medical report and phone call. Cardiovascular outcomes (death, Target Vessel Revascularization (TVR), MACCE) and stent thrombosis (ARC definition) rates were compared, according to total stent length, in patients with 1) BMS and 2) DES.
Results: 4335 PCI were performed in 4216 patients. Mean age was 65±12 years, 28% had diabetes, 91% had radial PCI, 32% had ACS. DES was used in 51%, BMS 44% and DES+BMS in 5%. Total stent length was 28±19 mm.
One year follow-up was completed for 98% of the patients. At one year, 8.8% (371) patients died, 9.2% (388) had TVR and 11.3% (476) MACCE, definite, probable and possible stent thrombosis occurred in 1.4%, 0.4%, 1.1%, respectively.
Unlike long BMS lengths, which are associated with higher mortality and MACCE rates ($p<0.001$ for both), long DES lengths don't carry any excess risk of death or MACCE (p=0.815 and p=0.234).
Stent length appears to strongly impact TVR and stent thrombosis rates in the BMS population, whereas this impact is much less evident in the DES population (Figure)

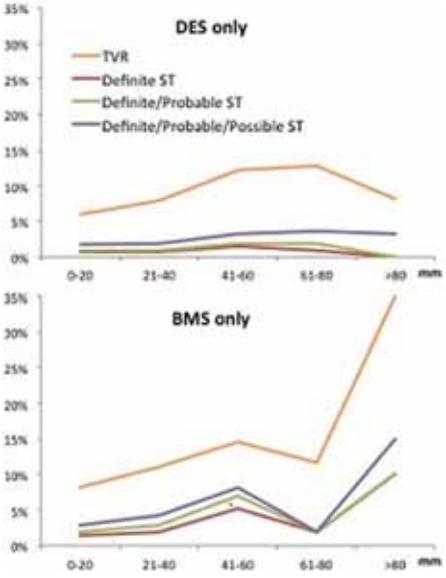

Figure 1. Events according to stent length (mm).

Conclusions: Long drug-eluting stent lengths aren't associated with an excess of stent thrombosis, new revascularization and CV events at one year compared to smaller ones, unlike BMS.

P5427 | BEDSIDE
Long term outcomes of percutaneous coronary interventions or bypass grafting surgery for left main coronary artery disease in octogenarians: a DELTA registry sub-study

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Purpose: Percutaneous coronary intervention (PCI) with drug-eluting stents (DES) is accepted as a feasible and safe alternative to surgery for the treatment of unprotected left main coronary artery (ULMCA) disease, but the long term clinical outcome in elderly patients is still unclear. Aim of our study was to compare the clinical outcomes of octogenarians with ULMCA disease treated either with PCI with DES or coronary artery bypass grafting (CABG).
Methods: The primary study endpoint was the composite of death, cerebrovascular accident and myocardial infarction at follow-up. Consecutive patients with ULMCA stenosis treated with PCI or CABG and age ≥80 years were selected and analyzed in a large, all comers, multinational registry.
Results: 304 patients were included: 218 were treated with PCI and 86 with CABG. During the hospital stay and at a median follow-up of 1,088 days the incidence of the primary endpoint was similar in the two groups (27.6% vs 31.1%, log-rank test: p=0.98). The incidence of target vessel revascularization at follow-up was higher in PCI patients (10.1% vs. 3.9%, log-rank test: p=0.05). At multivariable analysis, the only independent predictor of the composite primary endpoint was left ventricular ejection fraction (HR 0.95, CI 95% 0.91-0.98, p=0.001). After adjustment with propensity score, the revascularization strategy was not significantly correlated to the incidence of the primary endpoint (HR 0.98, CI 95% 0.57-1.71, p=0.95).
Conclusions: In octogenarians no difference was observed in the occurrence of the primary composite endpoint after PCI or CABG for the treatment of ULMCA disease. However, the rate of TLR was higher in the PCI group.

P5428 | BEDSIDE
Pre-treatment with high-dose atorvastatin in patients undergoing percutaneous coronary intervention: long-term follow-up of the ARMYDA (Atorvastatin Reduction for MYocardial Damage during Angioplasty)

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Purpose: The ARMYDA (Atorvastatin Reduction for MYocardial Damage during Angioplasty) group designed a series of randomized studies to investigate the effectiveness of statin pre-treatment in patients undergoing percutaneous coronary intervention (PCI). In the ARMYDA and ARMYDA-ACS studies, a reduced incidence of peri-procedural myocardial damage has been demonstrated in patients with both stable and unstable syndromes receiving high-dose statins. In the ARMYDA-RECAPTURE trial, an acute atorvastatin reload, in patients already on statins at the time of PCI, was associated with a significant improvement on 30-day clinical outcome. However, nowadays, no data are available on the possible beneficial effects of high-dose statin treatment before stenting on long-term outcomes. Thus, the aim of this analysis was to investigate this issue performing a clinical follow-up of all these above-mentioned trials.
Methods: The overall population included 479 patients from ARMYDA, ARMYDA-ACS and ARMYDA-RECAPTURE trial; 237 patients received high-dose atorvastatin pre-treatment and 242 placebo. On long-term follow-up, the occurrence of major adverse cardiac events (MACE), defined as death, acute myocardial infarction, target vessel revascularization and coronary artery bypass graft, was evaluated. As secondary end point, we analyzed the incidence of clinically driven in-stent restenosis (ISR).
Results: Clinical follow-up (mean 78±18 months) was successfully completed in 396 patients (83%). The primary composite end-point occurred in 20% (48) of patients receiving statin treatment and in 31% (75) of those not pre-treated (p=0.007). The incidence of ISR was 8% in the atorvastatin group vs 18% in the placebo arm (p=0.0015). Furthermore, the Kaplan-Meier curves showed an event-free survival of 78% in patients undergoing statin therapy and 66% in controls (p=0.035).
Conclusions: According to the ARMYDA trials, high-dose atorvastatin therapy before PCI may be strongly suggested both in statin-naïve patients and in those already on chronic statin use, in order to prevent peri-procedural myocardial damage. Moreover, for the first time, on the basis of the results of this analysis, an adjunctive improvement was observed also on long-term follow-up, with a reduced incidence of MACEs and ISR. All these evidences should definitely influence clinical practice and warmly support early initiation of statin therapy before PCI.

P5429 | BEDSIDE
Bundle branch blocks and outcomes in STEMI patients treated with primary PCI

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Purpose: Bundle branch blocks (BBB) have been associated with increased mortality in ST-elevation myocardial infarction (STEMI) patients treated with fibrinolysis. We sought to assess this relationship in STEMI patients treated with primary percutaneous coronary intervention (PCI).
Methods: A prospective cohort of 2349 patients undergoing primary PCI for treatment of STEMI from Jan 1, 2007 to Dec 31, 2012 were recruited into the study. Electrocardiograms (ECGs) were obtained at the time of presentation either with paramedics or in the emergency department. Old ECG's from 1996 until presentation were obtained for patients with BBB to determine if the BBB previously existed. For patients with left bundle branch block (LBBB), only those with inappropriately concordant ST changes were included. Mortality data was obtained through hospital and provincial mortality records. Using patients with a QRS interval of <120ms as a reference, odds ratios (ORs) for 30-day and 1-year mortality were calculated for different BBB types. Adjustment for age and co-morbidities was performed.
Results: Overall 30-day and 1-year mortality were 3.79% and 7.11%, respectively. 30-day mortality for patients with narrow QRS was 2.71%, RBBB was 13.9% ($p<0.0001$ versus narrow QRS), and LBBB with inappropriate ST-concordance was 19.4% ($p<0.0001$ vs. narrow QRS). 1-year mortality for narrow QRS was 5.4%, RBB was 23.7% ($p<0.0001$ vs. narrow QRS), and LBBB with inappropriate ST-concordance was 30.6% ($p<0.0001$ vs. narrow QRS).
For patients with RBBB (n=173), the ORs for 30-day and 1-year mortality were 5.78 (95%CI 3.49-9.57) and 5.47 (3.67-8.14), respectively; and 4.31 (2.53-7.36) and 4.13 (2.71-6.31) after adjustment. In patients with confirmed new transient or persistent RBBB (n=102), the adjusted ORs for 30-day and 1-year mortality were 5.62 (3.06-10.31) and 4.66 (2.80-7.77), respectively.
For patients with RBBB and anterior STEMI (n=105), the adjusted ORs for 30-day and 1-year mortality were 6.68 (3.34-13.34) and 4.87 (2.90-8.20). For patients with RBBB and inferior STEMI (n=58), the adjusted ORs for 30-day and 1-year mortality 2.70 (1.02-7.15) and 3.09 (1.45-6.61), respectively.
For patients with LBBB and inappropriate ST-segment concordance (n=36), the OR for 30-day and 1-year mortality were 8.67 (3.64-20.59) and 7.74 (3.72-16.14), respectively; and 4.88 (1.89-12.55) and 4.79 (2.14-10.75) after adjustment.
Conclusions: In patients treated directly with PCI, the presence of LBBB with inappropriate ST-segment concordance or development of a new RBBB in STEMI is predictive of increased 30-day and 1-year mortality.

P5430 | BEDSIDE
PCI vs CABG for multivessel disease in des era, systematic review and metanalysis

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The strategies of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) for revascularization have been compared in randomized clinical trials, however questions persist concerning the comparative effectiveness of both interventions.
Objective: To compare the safety and efficacy of PCI with DES vs CABG in the population of patients with multivessel disease.
Methodology: A systematic review and meta-analysis of randomized clinical trials (RCTs) was conducted, RCT comparing PCI using DES vs CABG with at least 12 months of follow up were included. The search was performed in Medline, Cochrane, EMBASE, CINAHL, OVID, LILACS,SCIELO.Two investigators extracted data independently on trial design, baseline characteristics, outcomes, and safety events from published manuscripts and unpublished supplemental data. The primary end point was a composite of all-cause mortality, myocardial infarction (AMI), stroke or the need of repeated revascularization after 12 months of follow up. The secondary end point was all-cause mortality and other individual cardiovascular events after 12 months and also the need of repeated revascularization after 3 and 5 years of follow up.Summary RRs and 95% CIs were calculated using a fixed and random model for combining results.The heterogeneity between studies were using Forest Plot and also by Cochrane Q considering heterogeneity as a p value lesser than or equal to 0.1 and I2 equal or higher than 50%. The risk of bias was evaluated by funnel plot.
Results: 1935 studies were screened for eligibility and 55 were identified for review, after excluding 51 studies, a total of 4 RCT with 4417 patients met r inclusion criteria for final meta-analysis (FREEDOM, CARDIA, SYNTAX, VA CARDS) All the trials analyzed in the study showed a low risk of bias (kappa=0.82). There was a significant difference in primary outcome in favor of CABG (RR 1.51 I C 95% 1.3-1.76) (I2: 0). A significant difference in myocardial infarction at 12 months (RR 1,51 CI 1.15 – 2.0) I2: 0) and repeated revascularization (RR 2,48 CI 2,0 - 3,01) (I2: 66.9) was also found in the CABG group, with non-significant reduction in mortality (RR 1,07 CI 0.79 – 1.44) (I2: 0). Stroke was less frequent in PCI group ((RR 0,35 CI 0.19 – 0.64) (I2: 0). A subgroup analysis was performed in diabetic population showing better outcomes in the CABG group.
Conclusion: CABG remains the standard of care for patients with multi vessel coronary disease, since the use of CABG, as compared with PCI, resulted in lower rates of the combined end point of major adverse cardiac at 1 year.

INTERVENTION BUT NOT THE CORONARIES

P5432 | BEDSIDE
Comparison of efficacy and safety of 4 different types nitinol wire mesh occluders in atrial septal defect closure

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Background: Interventional closure of atrial septal defects (ASD) became a standard treatment in the past two decades. It was achieved thank to new nitinol wire mesh occluders – Amplatzers. In recent years, however, other very similar occluders were introduced into clinical practice.
Purpose: To compare efficacy and safety of 4 different nitinol wire mesh occluders – Amplatzer Septal Occluder, Cardio-O-Fix, Figulla and Life Tech devices in simple ASD closure.
Material: Between the years 1997 and 2013, 963 patients diagnosed with single ASD had had interventional closure performed in our center. There were 806 patients closed with Amplatzers, 77 with Figulla, 55 with Cardi-O-Fix and 25 with Life Tech (Cera and HeartR devices).
Results: In all 963 patients ASD was closed. There were 8 early implant embolization – 7 Amplatzer and 1 Figulla devices – mainly in the early years of procedure experience. There were no significant differences between patients ASD size in TEE, implant size and fluoroscopy time in all type of implants. In the Amplatzer group the age and the weight of the patients were lower. No serious complications in follow-up were observed in any patient (as wall erosions, fracture of the device or thrombus formation), but observation time were shorter in non Amplatzer groups.

Table 1. Clinical and procedural data

Implant type	Age, years (mean)	Weight, kg (mean)	ASD in TEE, mm (mean)	Implant size, mm (mean)	Skopy, min (mean)
Amplatzer	0,5–77 (21)	6–129 (44,7)	4–34 (13)	5–40 (17,6)	0,5–39 (4,6)
Figulla	3,4–77 (34)	10–120 (53,2)	6–34 (16)	12–40 (22,5)	1–10 (3,2)
Cardi-O-Fix	3–72 (27),1	15–85 (55,2)	7–22 (13,9)	9–30 (18,8)	1,2–8 (3,37)
Cera+ HeartR	5,5–73 (30,6)	18–107 (56,8)	7–26 (13,8)	10–26 (17,5)	2–9,3 (3,7)

Conclusion: The use of all types of nitinol wire mesh occluders has the same effectiveness and all implant can be used exchangeable. The only advantage of smallest sheath sizes may promote Amplatzers in the closure of ASD in small children.

P5433 | BEDSIDE
The IOCVA method: a possible solution for placement of transvenous leads across total chronic occlusions

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Background: Placing a transvenous cardial lead is a challenge in the presence of bilateral venous obstruction of the upper extremities. Alternate access options, such as switching to the contralateral side or thoracotomy approach, exist but are associated with greater morbidity and less efficiency. Elayi et al recently described a promising novel method of vascular access that allows endocardial implantation of a defibrillation lead on the side of the venous occlusion.
Objective: The purpose of this study is to show the feasibility of the inside-out central venous access (IOCVA) method to gain vascular access in patients with complex central venous occlusions.
Methods: Four patients with central venous occlusions were referred for device implantation. Inside-out central venous access (IOCVA) was obtained via a percutaneous femoral approach. A catheter-dilator system was advanced via the right atrium to the most central point of venous occlusion. The occluded vein segment was punctured with a directionally guided needle, which was advanced along intravascular or extravascular tissue planes to the subclavian region. A solid wire needle was oriented toward the skin surface and advanced through the soft tissues until it exits from the body. The wire was used to pull rigid dilators through the occluded segment. Standard transvenous leads were implanted through the newly created channel.
Results: From May 2013 till December 2013, 4 patients were implanted using the IOCVA method. The mean age was 74 years, there were 3 males and 1 female. It was an initial implantation in all patients and all of them had a total central venous occlusion. They all had successful prepectoral device implants on the left side (3 ICDs and 1 CRT-D). Fluoroscopy and procedural times were longer than average. No procedure related complications occurred. All patients had normal device function at follow-up of 5,5 months.
Conclusion: IOCVA is a feasible method to implant a transvenous lead for patients with ipsilateral central venous occlusions. Although taking more procedural time and using more fluoroscopy, this method avoids switching to a de novo implantation on the contralateral side or obviates the need for a thoracotomy approach.

P5434 | BEDSIDE
Five-years single center experience with CoreValve transcatheter aortic valve implantation

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Background: Transcatheter aortic valve implantation (TAVI) has been designed to treat patients affected by severe symptomatic aortic stenosis considered extremely high risk for surgery candidates. We report a single centre 5-year experience with Medtronic CoreValve implantation in patients affected by severe aortic stenosis
Methods: Between May 2008 and December 2013 at our department 245 patients have been treated with transcatheter aortic valve implantation, 204 patients (mean age 80.3±11.2 years, 92 male) underwent Medtronic CoreValve implantation. All patients were judged high risk for standard aortic valve replacement (mean Euroscore II 10.7±10.2%, mean STS Mortality 9,3±6.5%). Fifty six patient were redo at TAVI, 40 underwent prior CABG. Forty four patient suffered by severe renal failure; 63% of patients suffered of peripheral vasculopathy
Results: All patients were evaluated and treated by a Heart Team composed by interventional cardiologist, hybrid cardiac surgeon, cardiac anesthesiologist and echocardiographist. 145 patients (71%) underwent trans-femoral TAVI and 51 patients were treated by a direct aortic approach. The CoreValve 26 and 29 was used in 92 and 94 patients respectively. Procedural mortality was 1 patient. Major vascular complication occurred in 27 patients (13.2%) and 34 patients experienced A bleeding complication. Forty patients required a permanent pace maker implantation. 30-day mortality was 5.3% (11 patients). Mean follow-up was 24.66±17.5 months, 44 (22,7%) died during follow-up with a 4-year survival of 63%
Conclusions: Our experience confirms that a real heart team approach to valvular disease, having the possibility to offer our patients different alternative access site, is the best way to treat TAVI patients getting excellent short and long term results

P5435 | BENCH
Immediate and midterm outcomes of repeat percutaneous mitral balloon commissurotomy for restenosis

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The increasing use of percutaneous mitral balloon commissurotomy (PMBC) has led to an increase in restenosis cases. Repeat PMBC may be a method of treatment for symptomatic patients with restenosis after successful initial one, but data regarding its outcomes are quite limited.
The aim of this retrospective study is to evaluate the immediate and midterm outcomes in patients who underwent a second PMBC for symptomatic mitral restenosis.
Methods: The study group consisted of 103 patients who have undergone a second PMBC, 4.5±3.3 years after a first intervention. All PMBC procedures were performed using the Inoue balloon system.
Results: The mean age of our patients was 28±11.2 years old and 78.8% were female. All patients present dyspnea with a poor functional capacity (New York Heart association [NYHA] III-IV). The wilkins score was between 8 and 12 in 60.2% of cases. The mitral valve area increased from 1.1±0.2 to 1.8±0.3 cm^2 and mean gradient decreased from 13±7.2 to 6.5±3.9 mmHg. An immediate good result (MVA $\geq$1.5 cm^2, mitral regurgitation $\leq$2) was obtained in 59 (57.28%) patients. There were no complications except for one case of pericardial tamponade requiring surgical evacuation (0.9%) and two cases (1.9%) of severe mitral regurgitation. The mean follow-up was 5±2.9 years. The 5-year restenosis and intervention (third PMBC or valve replacement) rates were 1.9% and 10.6%, respectively. The 5-year survival in good functional capacity (NYHA I-II) was 87.3±3.5%.
Conclusions: Repeat PMBC is a safe therapeutic option with good immediate and long-term results in patients with restenosis.
Repeat PMBC should be considered as the first treatment in suitable patients.

P5436 | BEDSIDE
Mobile echogenic images during 3D-transoesophageal intraprocedural monitoring of transaortic valve implantation: incidence, characteristics, and clinical implications

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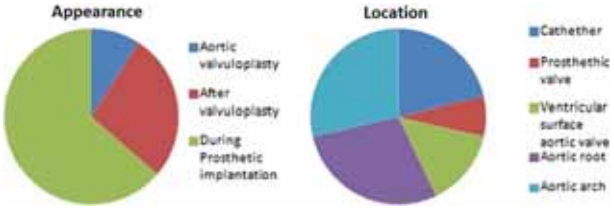
Background: Transaortic valve implantation (TAVI) is an alternative to surgical valvular replacement in high-risk patients with aortic stenosis. Transoesophageal (TOE) intraprocedural monitoring is highly recommended to position appropriately the prosthetic valve. Mobile echogenic images (MEI) may be visualized during the procedure, but information about this finding is scarce.
Material and methods: 104 consecutive patients undergoing TAVI (Edwards-Sapiens device) were included. All of them were monitored with 3D-TOE (Phillips). MEI were evaluated and correlated with clinical findings. All patients were fully anticoagulated (initially 100U/kg Sodic Heparin) and the procedure was performed following the standard protocol.
Results: MEI were visualized in 11 patients during the procedure (11%). In 7 cases (64%), MEI were seen during valve implantation and its main location was the aortic root (n=4; 36% Picture 1). Its size ranged between 3 and 30 mm, 45% of them had echocardiographic calcium density and 45% disappeared before procedural conclusion. The physician who performed TOE interpreted the MEI as thrombus in 55%, and as part of the former valvular structures in 45%. 3 of 104 patients had peri-procedural stroke, but MEI had been visualized in only one of them. No systemic embolisms occurred.



Location and appearance of MEI.

Conclusions: The visualization of MEI by 3D-TOE during TAVI is frequent, and in >50% of cases have echocardiographic characteristics of thrombus. The clinical implications of this finding is unclear.

P5437 | BEDSIDE
TAVI: comparison of multislice computed tomography and rotational angiography based 3D reconstruction imaging for the measurement of the fitting angulation for the aortic valve prosthesis implantation

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Purpose: During transcatheter aortic valve implantation (TAVI) the valve has to be placed exactly in the annulus of the aortic valve to avoid paravalvular aortic insufficiency or even dislodgement from the annulus. As implantation is guided by projection images the angiographic view should be orthogonal to the plane of the aortic annulus. We evaluated if this view could be sufficiently predicted by mulitislice computer tomography (MSCT) carried out before TAVI.
Methods: In 100 consecutive patients receiving transfemoral TAVI using a Medtronic CoreValve, MSCT Siemens Somatom Sensation was performed before TAVI and rotational angiography based 3D reconstructions (Siemens DynaCT) during TAVI. For both CT scans a plane was calculated which was perpendicular to the plane of the aortic annulus (defined as the plane through the most distal point of all three aortic cusps) and in which the noncoronary cusp was on the right, the left coronary cusp on the left, and the right coronary cusp in between. Differences of the angles of the angiographic view in left anterior oblique (LAO)/right anterior oblique (RAO) and caudal/cranial were calculated as well as the angle between the two planes from the scalar product.
Results: All MSCT had a sufficient quality for analysis, 2 DynaCT could not be analyzed due to artefacts from very severe calcification of the aortic annulus and breathing artefacts. The angles of the projections were LAO/RAO 6±16° (LAO 0–33°, RAO 0–20°) and cranial/caudal -12±17° (cranial 0–24°, caudal 0–25°) for DynaCT. The correlation to MSCT was 0.76 for LAO/RAO ($p<0.0001$) and 0.77 for caudal/cranial ($p<0.0001$). The differences in the projection angles were on average small but showed large variations:
The angle between the planes calculated by MSCT and DynaCT was 9.05±3.11° (0–14.86°). Considering an annulus of e.g. 25 mm, this angle is translated into a blurring of the annulus line using MSCT values for the projected image of 3.98 mm. This is half of the completely circular covered ring of the CoreValve which has a height of 8 mm.
Conclusion: The view needed for TAVI to view the aortic annulus on a line varies substantially among patients. If the view is predicted by MSCT carried out before TAVI a substantial error in relation to the valve height can occur. This may cause valve implantations which are too high or too low.

P5438 | BEDSIDE
Mitral regurgitation following percutaneous mitral balloon valvuloplasty: our experience

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Background and objective: Percutaneous mitral balloon valvuloplasty (PMBV) has revolutionized the treatment of patients with symptomatic mitral stenosis and is now established as the procedure of choice. Despite high technical expertise in PMBV using the Inoue balloon, mitral regurgitation (MR) remains a major procedure-related complication. We retrospectively analyzed our data of PMBV using the Inoue balloon with regard to the incidence of MR, its likely causative mechanism, and follow up of these patients.
Methods: During the past 15 years, PMBV was performed in 488 patients (me-

dian age 34, 15±12.9 years; range: 8-75 years). Transthoracic echocardiography with color flow mapping was performed before and 24 hours after the procedure
Results: Preprocedure mitral valve area (MVA) was 0.9±0.21 cm^2 (range: 0.5-1.5 cm^2); MR was mild in 178 cases (36.47%) and moderate in 21 (4.5%).
The procedure was successful in 396 (81.15%), with post-procedure MVA of 1.88±0.4 cm^2 (range: 1.4-3.2 cm^2), and without development of any major complication. Severe MR was seen in 19 patients (3.9%), of whom 11 (2.2%) required urgent mitral valve replacement (MVR). Echocardiography in these latter patients showed leaflet rupture. Eight patients (1.6%) with severe MR post PMBV were followed with medical treatment. Moderate MR was seen in 72 cases (14.75%). Severity of MR worsened in 38 cases (7.5%), of which 27 required elective MVR at a median follow up of 79±52 months. Univariate analysis showed that atrial fibrillation, mean mitral gradient immediately after PMBV were associated with mitral valve replacement.
Conclusion: Significant MR (moderate or severe) after PMBV was seen in 91 patients (18.64%), of whom 38 (7.78%) required MVR urgently or on follow up. All patients with leaflet rupture during PMBV developed severe MR and required urgent MVR.

P5439 | BENCH
Increased genome instability in AZFc region on Y chromosome in interventional cardiologists exposed to chronic ionizing radiation

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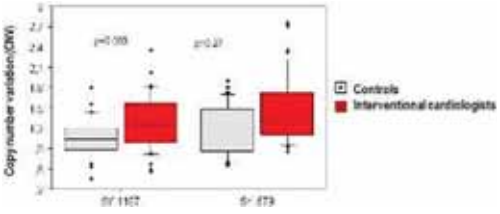
Backround- Occupational exposure in catheterization laboratory may cause damage to the reproductive system with adverse implications for fertility and reproductive outcome. Genomic instability in azoospermia factor region c (AZFc) is an important factor causing impaired spermatogenesis and susceptibility of this region in exposure to natural background radiation has been shown previously.
Aim: To investigate the possible induction of copy number variation (CNV) in AZFc region in male interventional cardiologists working in high-volume cardiac catheterization laboratory and exposed to chronic doses of ionizing radiation.
Methods: A group of 45 interventional cardiologists (47±9.6 years) and 32 unexposed controls (48.9±8.2 years) were enrolled in the study. Interventional cardiologists were occupationally exposed to ionizing radiation for 16.2±9.4 years (range 5–46 years). Two sex-determining region Y (SY) markers (SY1197 and SY579) in AZFc region and two housekeeping genes (GAPDH, β-globin) were assessed using genomic DNA extracted from leukocytes by quantitative Real-Time PCR. The copy number for each target was determined by the 2-ΔΔCT method.
Results: Elevated levels of CNV in SY1197 were found in exposed when compared to controls (1.29±0.39 vs. 1.05±0.29, p=0.003). As shown in Figure, no significant difference was found for SY579 marker (1.44±0.48 vs. 1.3±0.66, p=0.27). The SY1197 marker did not show correlation with age (p=0.11) and smoking (p=0.8). On the contrary, there was a positive linear relationship between years of exposure (r=0.331, p=0.02) and CNV in SY1197 markers.



Conclusion: Y-chromosome instability was remarkably high in invasive cardiologists, suggesting that occupational exposure may predispose to spermatogenic impairment.

P5440 | BEDSIDE
Percutaneous left atrial appendage occlusion with Amplatzer devices in high risk patients with atrial fibrillation and a contraindication to oral anticoagulation

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Purpose: Percutaneous left atrial appendage occlusion (LAAO) is evolving as a device therapy for reduction of thromboembolic risk in atrial fibrillation (AF). Most available data for LAAO are related to AF patients who have a moderate stroke risk and no contraindication for long-term oral anticoagulation (OAC). We report our initial single-center experience on LAAO in AF patients with a high stroke risk and a contraindication to OAC.
Methods: In the period from 2010-2013 we performed 50 LAAO procedures using the Amplatzer Cardiac Plug (ACP, n=37) or the Amplatzer Amulet (n=13). All patients had a contraindication to OAC most of them because of a previous serious intracerebral or gastrointestinal bleeding. Cardiac CT and transesophageal echocardiography was performed at 6 weeks and 12 months after the procedure.
Results: The mean age was 73 (28-91) and 72% were men. The mean CHA2DS2-VASc score was 4.9 (predicted stroke rate 6.6%/yr) and the HAS-BLED score 4.2 (predicted bleeding rate 8.8%/yr). Mean follow-up was 335 days; 45.9 patient years. Antithrombotic treatment after LAAO was aspirin 75 mg daily for 6 months. The mean procedure time was 70 minutes. The LAA closure success rate was 100% (50/50). The peri-procedural complication rate (<7 days) was 2/50 (4%). One patient had a device embolization. The device was easily snared and a new device was implanted without complications. Another patient with cerebral amyloid angiopathy suffered a small cerebral bleeding the day after the procedure. She recovered rapidly and completely. There were no episodes of pericardial effusion and no major peri-device leaks. We observed a thrombus on the proximal disc of an ACP 3 weeks after implantation. It resolved after 3 weeks on warfarin. One stroke was observed 4 months after the procedure in a diabetic patient with late stage complications including severe carotid atherosclerosis. The observed annual stroke rate was 2.2% (67% reduction vs. predicted) and the observed bleeding rate was 4.3% (51% reduction vs. predicted).
Conclusions: LAAO using Amplatzer closure devices is a safe novel transcatheter therapy that reduces the risk of stroke and bleeding in patients with a high thromboembolic risk and a contraindication to OAC.

P5441 | BEDSIDE
Frequency and prognosis of stroke after transcatheter aortic valve implantation

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Transcatheter aortic valve implantation (TAVI) has emerged as an alternative to surgical aortic valve replacement for patients considered at high or prohibitive operative risk, however recent studies have raised major safety concerns because of increased risk of stroke/transient ischemic attack (TIA) rates with TAVI compared to medical treatment and conventional aortic valve replacement. The aims of this study were to report the frequency of stroke and its relation to the clinical outcome after TAVI.
Methods and results: Between April 2008 and December 2013, 372 patients with symptomatic aortic valve stenosis who were considered high risk or non surgical candidates underwent implantation with the CoreValve prosthesis. Stroke was defined according to the Valve Academic Research Consortium recommendations. The mean age of patients was 79.2±6.3 years and the mean logistic Euro SCORE of 18.17±12%. 13 patients had stroke (3.5%). Procedural stroke <24 h occurred in 46% after percutaneous valve implantation. Factors associated with the occurrence of stroke were previous presence of TIA [46.2% vs. 13.1% OR 5.69 (95% CI 1.83-17.6, p<0.001], and prior pacemaker [30.8% vs. 7%, OR 5.9 (95% CI 1.7-20.5) p=0.002], and ejection fraction (52±8 vs. 60±15, p=0.008).
In the multivariate analysis, the only independent factor for stroke after percutaneous valve implantation was the presence of TIA (HR 5.016 95% CI 1231 to 20.439, p 0.024). Hospital mortality associated with the presence of stroke was very high 23.1% vs. 3.6%, p=0.001.
Conclusions: The stroke/TIA in patients undergoing TAVI with the CoreValve prosthesis is a serious and rare complication. The occurrence of stroke was associated with increase early mortality

PCI DIFFERENT DEVICES

P5443 | BENCH
A novel bioabsorbable scaffold scaffold on PLLA/ACP is superior than PLLA bioabsorbable scaffold in process of endothelialization

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Purpose: Bioabsorbable scaffold has been applied in clinic in recent years and manifested a good safety and efficacy because of its biocompatibility. In present study, a novel bioabsorbable scaffold based on poly-lactic acid (PLLA) combined with amorphous calcium phosphate (ACP) was compared with a traditional bioabsorbable scaffold based on PLLA alone on endothelial formation and function.
Methods: A total of 12 PLLA or PLLA/ACP (half to half) based paclitaxel-eluting scaffolds were randomly implanted into the coronary arteries from 12 healthy pigs. At the 28th day after scaffold implantation, coronary angiography was applied to all pigs. Then these pigs were sacrificed, and the arteries with scaffolds were taken off before collection of serum. The segments with scaffold were used to calculating inflammation score and endothelialization score by scanning electron microscopy (SEM). To evaluate endothelial formation and inflammatory state, the expressions of endothelial nitric oxide synthase (eNOS), CD31 and NF-κB were detected by immunohistochemical assay. In addition, serum nitric oxide (NO) level

and vascular endothelial growth factor (VEGF) level were determined by corresponding ELISA kits in order to assess the endothelial function after scaffold implantation.
Results: At the 28th day, no in-scaffold restenosis or scaffold thrombosis were found in both PLLA and PLLA/ACP group. Histological analysis from SEM indicated that the inflammation score in PLLA/ACP group was less than that in PLLA group (1.20±0.42 vs. 1.70±0.48, P<0.05). Consiscaffold with that, the expression of NF-κB was lower in PLLA/ACP group (22.07±3.18 vs. 28.59±3.54,P<0.05). The endothelialization score was higher in PLLA/ACP group than that in PLLA-group (2.00±0.47 vs. 1.40±0.52, P<0.05), even though no significant difference was found in neointimal area percentage between these two groups. The levels of VEGF and NO in PLLA/ACP group were significantly higher than those in PLLA group respectively (309.86±49.37 pg/ml vs. 222.04±55.16 pg/ml and 129.96±9.52 μmol/L vs. 79.55±16.55μmol/L, P<0.05). The results from immunohistochemistry showed that the expressions of eNOS and CD31 in PLLA/ACP group were dramatically higher than those in PLLA group respectively (38.53±4.25 vs. 27.53±3.55, P<0.01; 29.40±3.84 vs. 19.78±3.50, P<0.05).
Conclusion: The application of ACP is helpful in endothelial formation and function for PLLA-based bioabsorbable scaffold, and this effect can be attributed to the reduced inflammatory reaction, at least partially.

P5444 | BEDSIDE
Indirect comparison of coronary artery bypass grafting vs percutaneous coronary intervention using new generation drug-eluting stents, a bayesian network meta-analysis

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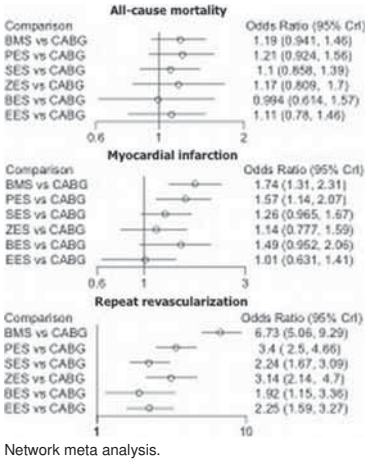
Background: As the technology advances, new generation drug-eluting stents (DES) are reported to have better clinical outcomes than bare metal stents (BMS) or 1st generation DES. However, there has been no trial using new generation DES in comparing coronary artery bypass grafting (CABG) vs percutaneous coronary intervention (PCI). We performed indirect comparisons between CABG vs PCI with new generation DES.
Methods: For the indirect comparison, we used Bayesian network meta-analysis. During systematic literature search, randomized trials comparing one intracoronary stents another were included as well as studies of CABG vs. PCI for treating left main or multivessel disease. (80,375 patients from 100 trials and 9,736 from 11 trials respectively). Comparisons were made for all-cause mortality, myocardial infarction (MI), repeat revascularization and stroke.
Results: With respect to mortality and MI, superiority of CABG was not significant, especially compared to new generation DES (figure). Regarding repeat revascularization, CABG was better than PCI, regardless of stent types. However, the benefit decreased from odds ratio (OR) 6.7 with BMS to OR 1.9 with biolimus eluting stent (BES, figure). In the direct comparison using trials of CABG vs. PCI, stroke was fewer in PCI group than in CABG group (OR 0.47, 95% credible interval 0.19~0.88).



Network meta analysis.

Conclusion: Benefit of CABG over PCI in morality and MI reduction seems uncertain. Although CABG was superior to PCI regarding repeat revascularization, the advance of stent technology has narrowed the gap. Randomized trials comparing CABG vs. PCI with new generation DES is required.

P5445 | BEDSIDE
Causes of longitudinal shortening of coronary stents: evaluation by multislice computed tomography

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Purpose: Concern has been raised regarding the longitudinal integrity of new drug-eluting stents (DES). This study sought to evaluate the mechanisms of longitudinal deformation of coronary stents by multislice computed tomography (MSCT).
Methods: This study included 45 stents that could have been potentially shortened by mechanical actions such as: 1) guiding catheter impingement; 2) post-dilation; 3) bifurcation techniques; 4) intravascular imaging techniques after stent implantation. MSCT was scheduled by protocol 9-12 months after the procedure. The primary endpoint was the relative change in stent length (length by MSCT divided by the stent length reported by the manufacturer).
Results: Stents subject to catheter impingement were more frequently stainless-steel DES whereas those subject to post-dilation tended to be more frequently platinum-chromium DES. Stents subject to catheter impingement were shortened more than those that did not (mean difference 7.6%, 95% CI 3-12%, p>0.01). There were no differences in longitudinal deformation with the other studied mechanical actions (figure). After adjustment by stent-alloy type and nominal stent length, catheter impingement was the only mechanical action associated to longitudinal deformation. No stent fractures were observed.

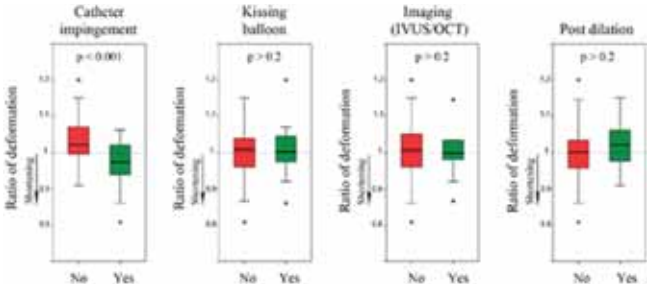

Figure 1

Conclusions: Guiding catheter impingement is the only mechanical action significantly associated to DES shortening. Therefore, it is of importance to avoid catheter impingement after stent implantation in coronary ostia independently of the stent type.

P5446 | BEDSIDE
Left main percutaneous coronary intervention (pci) improves lv systolic function by tissue doppler imaging (tdi) echocardiography

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Purpose: Prevalence of left main (LM) percutaneous coronary intervention (PCI) has increased all over the world and showed its favorable clinical outcome. However, whether left main PCI improves left ventricular function or not has not been fully clarified yet.
Methods: From October 1996 to March 2012, 164 patients underwent left main PCI at our institution. Twenty four patients who had both tissue Doppler image (TDI) echocardiography exams of pre and post LM PCI were included this study. We compared echocardiographic findings including TDI of pre and post LM PCI.
Results: Time interval between PCI and post-PCI echocardiography was 85.9±87.9 days.

Echocardiographic data pre and post PCI

	Pre LM PCI	Post LM PCI	
LVEF (%)	45.2±16.2	49.3±15.2	0.024
LVDd index	31.8±6.0	32.3±7.1	0.712
LVDs index	24.0±7.1	23.5±6.2	0.619
EDV index	83.3±33.0	80.3±25.1	0.606
ESV index	45.3±31.4	40.5±22.3	0.314
SV index	38.1±12.9	39.9±13.4	0.434
TDI			
Systolic velocity (S')	5.7±2.0	6.9±2.0	0.006
E'	7.2±3.9	6.7±2.2	0.572
A'	8.5±2.6	9.4±2.8	0.251
E'/A'	0.8±0.3	0.7±0.3	0.386
E/E'	14.8±10.9	13.9±9.6	0.55

Left ventricular ejection fraction (45.2±16.3 vs. 49.3±15.3%, P<0.05) and septal systolic velocity (S') measured by TDI (5.7±2.1 vs. 6.9±2.0, P<0.01) were significantly improved after LM PCI (Table).
Conclusions: LM PCI improves LV systolic function not diastolic function assessed by TDI echocardiography.

P5447 | BEDSIDE
Biolimus-A9 eluting stent implantion for unprotected left main coronary artery stenosis: 9-month strut coverage as assessed by optical coherence tomography

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Aims: To evaluate strut coverage after biolimus-A9 eluting stent (BES) implan-

tation for unprotected left main artery (ULMA) stenosis and identify features associated with the length of uncovered stent segment, as assessed by frequency domain-optical coherence tomography (FD-OCT)

Methods and results: We prospectively enrolled 32 patients with ULMA stenosis treated with BES. FD-OCT were performed at 9-month follow up. Both malapposed and uncovered segment length were indexed for the segment between the distal and proximal cross-sections in which stent struts were circumferentially visible. Patients were divided into 2 groups according to the median value of maximal indexed-uncovered segment length. Study endpoints were the rate of strut coverage and predictors of high uncovered segment length. We analyzed 3622 struts. The rate of covered struts was 87%. A high correlation was found between malapposed and uncovered segment length (r=0.82,p<0.001) [Figure]. The median value of indexed-uncovered segment length was 0.308. On multivariable analysis, patients undergoing final kissing balloon were at lower risk of high uncovered segment length (OR=0.81;95%CI 0.008-0.837,p=0.035).

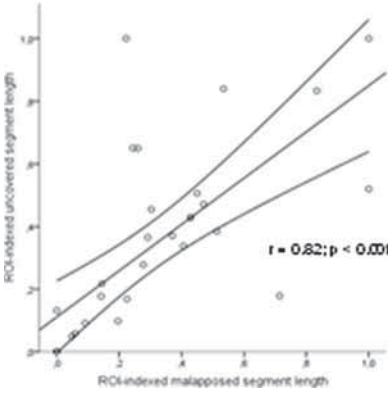

Figure 1

Conclusion: In patients undergoing BES implantation for treatment of LMA stenosis the rate of 9-month strut coverage is high. The use of final kissing balloon reduces the risk of high uncovered stent segment length

P5448 | BEDSIDE
Patient and operator radiation dose using a pelvic lead shield during trans radial angiography

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Background: Cardiac angiography using the radial access compared to the femoral approach, is associated with reduced complication rate and improved patient comfort but has significantly increased radiation dose to the patient and the operator. Improvements in radiation protection are needed. Pelvic lead shielding has the potential to reduce operator radiation dose.

Aims: To determine the efficacy of a 0.5-mm lead apron across the patient's abdomen in addition to standard operator protection for the reduction of scatter radiation on operator radiation exposure and to measure also patient radiation dose.

Methods: We randomly assigned 202 patients undergoing coronary angiography to a group with pelvic lead shielding and a group without. In each procedure 8 dosimeters were used to measure operator radiation dose [under the lead apron, outside the thyroid shield and at the left side of the head] patient dose at the level of the umbilicus [above and beneath the lead apron] and 2 on the acrylic shielding and one on the image intensifier to measure scattered radiation.

Results: Both groups were similar in BMI, procedures performed and number of sequences. Usage of lead shielding statistically significantly reduced the radiation dose of the operator at all 3 sites measured: under lead apron: 0.02±0.05 Vs. 0.06±0.17, on thyroid collar: 0.37±0.35 Vs. 0.64±0.79 and left side of head 0.24±0.21 Vs. 0.36±0.35. However the radiation for the patient was doubled 3.9±10.95 Vs. 1.51±2.65, p<0.001.

Conclusions: The use of a pelvic lead shield during radial angiography reduced the operator radiation exposure at multiple measurement sites. However there was an increased exposure to the patient. This balance has to be further investigated before the widespread of this method.

P5449 | BEDSIDE
The incidence, clinical outcomes, and risk factors of peri-contrast staining after second generation des implantation

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Background: Several studies showed peri-contrast staining (PSS) after silorimus-eluting stent was be associated with target-lesion revascularization (TLR) and very late stent thrombosis. However, the incidence and clinical sequela of PSS after second generation DES implantation are unclear, so we retrospectively evaluate the clinical outcomes.

Methods: This study consisted of de novo 2185 lesions in 1734 patients that were treated with second generation DES (zotarolimus-eluting stent: ZES, everolimus-eluting stent: EES, and biolimus-eluting stent: BES). They were evaluated by follow-up angiography within 12 months after stent implantation, from April 2009 to December 2012. We divided into PSS group and non-PSS group and compared the two groups in clinical and angiographical outcomes.

Results: We had obtained 1826 lesions follow-up angiography. (83.6%) The mean clinical follow up period was 788±15 days. Baseline clinical and angiographic characteristics were similar between the two groups. (N.S.) Late acquired PSS was observed in 19 lesions (0.87%) in 17 patients (0.98%). In these lesions, 3 lesions (0.73%) were observed in BES, 9 lesions (0.67%) were EES and 7 lesions (1.62%) were ZES. (N.S.) Stent fracture (SF), tortuosity, and lesions with severe angulation (>45°) were more frequently observed in lesions with PSS than in lesions without PSS (18.2% versus 0.61%, p<0.0001, 7.1% versus 0.85%, p=0.03, 0.85% versus 6.9%, p=0.03). Cumulative incidence of TLR and MACE in the PSS group was higher than that in the non-PSS group. (41.2% versus 6.0%, and 47.1% versus 9.6%, p<0.0001). There was no significant difference in late and very late stent thrombosis between the two groups. (N.S.)

After multivariable analysis, CTO (OR: 4.07, 95% CI: 1.1 to 12.1, p=0.04), and reference diameter (>2.83mm) (OR: 4.17, 95% CI: 1.5 to 12.4, p=0.005) were independent predictors for PSS.

Conclusions: PSS after second generation DES was a rare phenomenon but appeared to be associated with subsequent TLR.

P5450 | BEDSIDE
Feasibility and angiographic 6-month follow-up of FFR-guided DEB-only elective coronary angioplasty (OCTOPUS II Study)

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Purpose: We investigated the safety and feasibility of fractional flow reserve (FFR) - guided use of drug-eluting balloons without stenting for elective PCI of de novo lesions.

Methods: In 49 consecutive patients (57 lesions) with stable symptomatic coronary artery disease (CAD) FFR-guided angioplasty (POBA) was performed. In case of a sufficient POBA result with FFR >0.8 and residual stenosis <40% without flow-limiting dissection, another dilatation of the target lesion was carried out using the DEB. Quantitative coronary angiography (QCA) was attempted before and after the index procedure and at 6-month follow-up (f/u), when the late lumen loss (LLL) and net luminal gain (NLG) were calculated.

Results: DEB-only concept could be applied to 46 patients (54 lesions), while 3 patients (3 lesions) needed provisional stenting. Invasive f/u was completed in 42 DEB-only patients (50 lesions). At the stenotic site, the lumen showed progressive increase at f/u (Fig. 1) without aneurysm formation or restenosis.

Table 1

	FFR	MLD (mm)	Stenosis (%)	LLL (mm)	NLG (mm)
Baseline	0.64±0.19	0.82±0.26	64±11	n/a	n/a
PCI result	0.91±0.06*	1.80±0.42*	29±11*	n/a	n/a
6-month f/u	not assessed	1.96±0.68*	21±21*°	–0.14±0.45	1.13±0.57

*p<0.05 vs. baseline, °p<0.05 vs. PCI result.

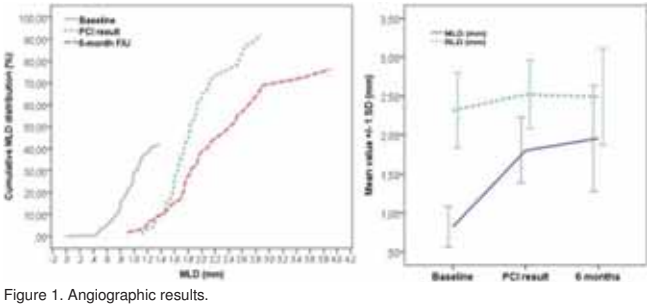

Figure 1. Angiographic results.

Conclusion: FFR-guided DEB-only treatment of de novo lesions in stable CAD is safe and feasible and allows to stop clopidogrel after 4 weeks. Paclitaxel delivery led to late luminal gain at 6-month f/u after DEB angioplasty without stenting.

P5451 | BEDSIDE
Mid-term results of bioabsorbable vascular scaffold for coronary lesions beyond stablished indications

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Purpose: Bioabsorbable vascular scaffold (BVS) is increasingly used in patients with coronary artery disease undergoing percutaneous coronary intervention.

However complex lesions have been excluded in most clinical trials. The aim of this study is to analyse the mid-term follow up of a cohort of patients with complex lesions treated with BVS.
Methods: From January 2012 to January 2014, 306 patients having 394 coronary lesions were treated with BVS in our institutions. From them, we analyse the subset of patients (n=197) with complex lesions (n=233).
Results: The mean age was 57±9 years;168 patients were male (85%). In 81 (42%) the clinical presentation was an acute coronary syndrome. The location of the lesion was as follows: Left anterior descending artery 127; Left circumflex 57; Right coronary artery 44 and Left main 5. The mean lesion length was 22.2±11 mm and the mean stenosis was 75±20%. Thirty-one lesions were chronic total occlusion, 155 bifurcation lesions, 9 restenosis lesions and 112 long diffuse stenosis (≥22 mm). In 64 cases (27%), the lesion shared at least 2 types of complexities. Nighty seven lesions (42%) were studied at baseline condition by intravascular ultrasounds (IVUS). After BVS implantation the geometry of the scaffold was analysed by optical coherence tomography in 80 lesions (34%) and with IVUS in 66 (28%). Direct BVS implantation was perfomed in 128 lesions (55%) and in the remaining 114 lesions preconditioning of the lesion by balloon angioplasty was carried out. The mean BVS diameter was 3.1±03 mm, and the mean scaffolded length was 26.5±12 mm. Primary angiographic success was obtained 233 lesions (100%). Ten patients (5%) had a periprocedural myocardial infarction. Mayor cardiac events at follow up was 2.5.%. After a mean follow-up time 11±5 months,84 patients (90 scaffolded segments) were studied by scheduled angio-CT scan, documenting two restenosis of the scaffold. Angiographic reevaluation driven by symptoms showed 3 additional restenosis. In all 5 restenotic lesions (2.5%) target lesion revascularization was performed. The remaining patients are symptoms free.
Conclusions: Treatment of complex lesions with bioabsorbable vascular scaffold is safe with a low rate of mayor adverse cardiac events at mid-term follow-up

P5452 | BEDSIDE
Impact of overlapping site on 9 month angiographic results after multiple overlapping everolimus-eluting stents implantation: a serial quantitative coronary angiography analysis

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Background: In the era of drug-eluting stents, multiple overlapping stents was performed more than 10% of patients with diffuse coronary artery diseases. However, correlation between the location of overlapping site and 9 month follow-up (FU) minimum lumen diameter (MLD) site after multiple overlapping everolimus-eluting stents (EES) was not well evaluated.
Methods: From the prospective, multi-center study of XILLION (XIence/promus for Long coronary LesION) registry to assess the efficacy of multiple overlapping EESs in patients with diffuse long coronary artery disease, serial quantitative coronary angiography (QCA) analyses at pre-, post-procedure, and 9 month FU were performed for pre-, post-procedural MLD, and overlapping sites. MLD site at FU angiography was independently evaluated by QCA analysis.
Results: A total of 330 patients with 348 lesions were enrolled and 9 month FU angiography was performed for all patients. In 52% of the lesions, the location of pre-procedural MLD was same as that of FU MLD. On the other hand, in 72% of the lesions, the location of post-procedural MLD was same as that of FU MLD. All same MLD sites (pre- = post-procedure = FU) were observed in 44% of lesions. New MLD site was observed at FU in 8% of lesions. MLD site was observed at overlapping site in 5.3% of the lesions at post-procedure and 1.4% at 9 month FU. No angiographic restenosis was observed at overlapping site. Angiographic data was shown in table.
Conclusion: After multiple overlapping stenting, overlapping site was not associated with the location of MLD at pot-procedure and 9 month FU. The location of MLD site at pre- and post-procedure correlated with at 9month FU.

P5453 | BEDSIDE
Impact of final kissing balloon inflation on vessel healing following drug-eluting stent implantation: insight from the optical coherence tomography sub-study of J-REVERSE trial

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Background: The impact of final kissing inflation (FKI) after single stenting to true bifurcation lesions remain unclear.
Methods: J-REVERSE is a prospective multicenter registry of cases treated with provisional stenting to bifurcation lesions with (n=30) or without FKI (n=34) using sirolimus- (SES) and everolimus-eluting stent (EES). The first 64 lesions at selected study sites were predefined for inclusion in the OCT sub-study and underwent 9-month follow-up OCT. Stent eccentricity index (SEI; minimum divided by maximum stent diameter) and neointimal unevenness score (NUS: maximum noeintimal thickness in the cross-section (CS) divided by the average NIT of the same CS) was averaged for each segment (proximal, bifurcation, and distal segment).
Results: At the proximal segment, FKI group had a significantly larger average stent area with a greater asymmetric stent expansion than non-FKI group. As a result, average lumen area remained significantly larger in FKI than in non-FKI 9 months after stenting, although FKI had a tendency toward a greater neointima proliferation than non-FKI. At the side branch orifice, the incidence of jailed strut was significantly lower in FKI than in non-FKI. At the bifurcation segment and the proximal segment, NUS was significantly smaller in FKI than non-FKI group, suggesting homogeneous neointimal proliferation afforded by FKI (Table).

	Proximal segment			Bifurcation segment		
	FKI group	non-FKI group	p-value	FKI group	non-FKI group	p-value
Average stent area, mm^2	8.18±1.8	6.89±1.61	0.004	6.94±1.81	6.46±1.6	0.266
Average neointomal area, mm^2	1.05±0.63	0.8±0.44	0.074	0.84±0.44	0.73±0.4	0.294
Average lumen area, mm^2	7.16±1.95	6.13±1.54	0.021	6.1±1.86	5.76±1.56	0.428
Average SEI	0.84±0.06	0.88±0.05	0.003	0.85±0.06	0.86±0.07	0.684
Average NUS	1.71±0.25	1.91±0.33	0.008	1.9±0.4	2.23±0.39	0.002
% Jailed strut, %	NA	NA	NA	6±7.5	14±8.8	<0.001

Conclusion: In the treatment of true bifurcation lesions, FKI offered less luminal narrowing in the proximal segment 9 months after stenting. Although a greater neointimal proliferation may occur in the proximal segment, a greater stent expansion seems to compensate such neointima growth. Considering homogeneous neointimal distribution and less jailed struts, FKI may be a beneficial option in the treatment of true bifurcation.

PCI LONG-TERM OUTCOME AND DRUGS

P5455 | BEDSIDE
Prospective multicenter registry of 6 months dual antiplatelet therapy after new generation drug-eluting stent implantation: ESTROFA-DAPT study

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Purpose: Drug-eluting stents (DES) have been related to a certain risk of late thrombosis. The recommended duration of dual antiplatelet therapy (DAPT) with DES is 12 months. DAPT is not free from complications and is expensive. Small trials suggest that a 6 month DAPT period could be enough with new generation DES. There are no large clinical registries assessing the safety of such approach.
Methods: All consecutive patients treated with non-first generation DES were prospectively included in 18 different centers. Patients had to fulfill one of the following inclusion criteria: silent ischemia, stable angina, low risk non-ST segment elevation myocardial infarction or acute coronary syndrome where 12 months DAPT was discarded due to high bleeding risk.

Abstract P5452 – Table 1. Serial angiographic analysis

	Post at pre MLD site	Post at post MLD site	Post at overlapping site	p	FU at pre MLD site	FU at post MLD site	FU at overlapping site	p
Number	348	348	424		348	348	424	
RVD, mm	3.04±0.39	3.01±0.39	3.06±0.35	0.86	2.97±0.41	2.94±0.41	3.01±0.36	0.32
MLD, mm	2.67±0.42	2.51±0.37	3.05±0.35	0.01	2.45±0.22	2.32±0.47	2.84±0.38	<0.0001
DS, %	11.9±7.4	16.2±6.5	1.07±0.07	<0.0001	18.1±10.3	16.2±6.5	18.1±10.3	0.22
Acute gain, mm	1.77±1.47							
Late loss, mm					0.22±0.29	0.23±0.63	0.21±0.27	0.89
Restenosis rate, %					3.6	1.6	0	

Post: post-procedure, Pre: pre-procedure, MLD: minimum lumen diameter, RVD: reference vessel diameter, FU: 9 month follow-up.

Results: A total of 1,024 patients have been included with age 67.5±10.6 years, 23.3% women, 41% diabetic and 25.8% with ACS. Among these 354 patients have already completed 12 months follow up. In this cohort the incidence of definite or probable thrombosis at 12 months was 0.57% (1 definite thrombosis at 2 months and 1 probable thrombosis at 7 months). The incidence of cardiac death and myocardial infarction at 12 months was 2.5%. Events reported between 6 and 12 months were 3 cardiac deaths (2 heart failure and 1 sudden death) and 2 non-ST elevated myocardial infarctions (one related with stent restenosis and the other without angiography considered a probable stent thrombosis). Using the ESTROFA-2 database (4,768 patients treated with new generation DES, 4,355 of them with 12 months DAPT) we performed a propensity score matching with this registry. In ESTROFA-2 the incidence of definite or probable thrombosis at 12 months under 1 year DAPT was 0.7%
Conclusions: A DAPT period of 6 months after non-1st generation-DES implantation in selected population results safe with a very low rate of events between the 6th and 12th month. Final follow up for the whole cohort will be available at the time of the congress.

P5456 | BEDSIDE
Long-term clinical impact of polymer-free sirolimus-eluting stents in unselected patients

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Purpose: The long-term clinical impact of polymer-free sirolimus-eluting stents (PF-SES) in unselected patients undergoing percutaneous coronary interventions (PCI) remains poorly investigated. We therefore sought to investigate the long-term clinical impact of PF-SES in a large cohort of unselected patients receiving PCI-therapy.
Methods: PCI-patients receiving PF-SES at two hospitals were retrospectively studied. The primary endpoint was major adverse cardiac events (MACE; death/myocardial infarction – MI – or target lesion revascularization – TLR). The secondary endpoints were the subcomponents of the primary endpoint, cardiac death/MI and definite/probable stent thrombosis (ST). A subgroup analysis evaluated the occurrence of MACE, TLR and cardiac death/MI according to gender, age, diabetes status, clinical presentation and multivessel disease.
Results: A total of 1,213 patients (males 83.8%, diabetics 31.8%) and 1,658 lesions (B2/C 52.5%) were studied. At a median follow-up of 1,160 days the incidence of MACE was 10.0% (119 patients), death 7.6% (92 patients), MI 3.2% (38 patients), TLR 2.2% (27 patients), cardiac death/MI 5.4% (65 patients) and definite/probable ST 1.9% (23 patients). MACE were more likely in patients aged ≥65 years (p=0.004), diabetics (p=0.004) and with unstable clinical presentation (p=0.042) without impact of gender (p=0.14) and multivessel disease (p=0.18). No difference in the occurrence of TLR was found according to gender (p=0.92), age (p=0.28), diabetes (p=0.47), clinical presentation (p=0.19) or multivessel disease (p=0.44). Cardiac death/MI was more likely in patients aged ≥65 years (p<0.001), without impact of gender (p=0.27), diabetes (p=0.30), clinical presentation (p=0.08) and multivessel disease (p=0.13).
Conclusions: This study reports a sustained safety and efficacy at long-term follow-up in the largest cohort of unselected PCI-patients treated with polymer-free sirolimus-eluting stents studied so far.

P5457 | BEDSIDE
Comparison of the safety and efficacy of bio-absorbable versus permanent polymeric platinum-chromium everolimus-eluting stents in real-world asian cohort

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Objective: Drug-eluting stent (DES) with bio-absorbable polymer has the potential safety benefit of reducing stent thrombosis while maintaining efficacy. This study aims to compare the safety and efficacy of the permanent polymeric platinum-chromium Everolimus DES with the newer generation bio-absorbable polymeric stent of the same alloy and drug.
Methods and results: A total of 320 patients, who were implanted with either stents in our centre while undergoing percutaneous coronary intervention (PCI), were enrolled in this retrospective study. The primary endpoints were major adverse cardiac events (MACE), defined as all-cause death, myocardial infarction (MI) and repeat revascularisation at 6 months. The baseline characteristics were similar with mean age of 59.3±0.61 years, 85.3% males and 34.7% diabetics. Majority of the lesions (96%) treated were AHA/ACC Type B2/C and the mean length of lesion was 24.9±10.7mm.

Incidence of MACE

	Bioabsorbable polymer DES (n=186)	Permanent polymer DES (N=134)	P value
Death, n (%)	2 (1.08%)	2 (1.49%)	0.74
MI, n (%)	0 (0.0%)	0 (0.0%)	–
Repeat revascularisation, n (%)	1 (0.54%)	2 (1.49%)	0.38
MACE, n (%)	3 (1.62%)	4 (2.99%)	0.41

The overall event rates were low at 6 months, with no significant difference in the overall MACE between the 2 groups. There was also no stent thrombosis.
Conclusions: The early experience with the new generation of bio-absorbable platinum-chromium DES suggests comparable efficacy to permanent polymeric DES with no safety concerns related to the biodegradable polymer.

P5458 | BEDSIDE
Impact of metabolic syndrome on clinical outcome after new-generation drug-eluting stent implantation

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Purpose: Metabolic syndrome (MetS) has been reported to have negative impacts on the clinical outcome of patients who underwent percutaneous coronary interventions (PCI) with even drug-eluting stents (DES). Recently, new generation DES have improved clinical outcomes. However, their impact on patients with MetS is still unclear and data is limited. Because of the improvements of DES, there might be changes in the impact of MetS on the clinical outcome of patients in the era of new-generation DES
Methods: A single-center retrospective cohort study was performed from 2009 to 2013. Subjects undergoing PCI in at least one coronary artery using everolimus-eluting stents were included. A composite endpoint included target lesion revascularization (TLR), target vessel revascularization (TVR) and stent thrombosis. The recommendations of the Third Report of the National Cholesterol Education Program Expert Panel were used for MetS criteria.
Results: Total 909 subjects were observed for 4.9 years. Of the subjects, 613 (67.5%) were male, 551 (60.6%) had hypertension, 307 (33.8%) had diabetes and 571 (62.8%) were diagnosed with MetS. The mean age was 64.8±10.7 years, total stent length (TSL) was 51.7±31.7 mm and the number of intervened coronary arteries was 1.5±0.7. All subjects took standard medical therapy including statin after the index procedures. Multi-vessel coronary artery disease (CAD) was more frequent and TSL was longer in subjects with MetS than those in subjects without MetS. Cardiac death and the composite endpoint occurred in 12 subjects (1.3%) and 88 subjects (9.7%), respectively. In Cox-regression analysis, the rate of cardiac death (1.4% vs. 1.2%, p=0.61), TVR (0.2% vs. 0.5%, p=0.61), TLR (8.3% vs. 7.4%, p=0.63) and the composite endpoint (10.0% vs. 8.6%, p=0.47) in subjects with MetS were not significantly different from those in subjects without MetS. After adjustment for age, sex and TSL, the rate of the composite endpoint in subjects with MetS was still not different from that in subjects without MetS (hazard ratio = 1.15, confidence interval 0.73-1.81).
Conclusion: Although the extent of CAD was greater in subjects with MetS, the presence of MetS seems to have little impact on the outcome of patients undergoing PCI in the era of second-generation DES.

P5459 | BEDSIDE
Readmission during the first year after percutaneous coronary intervention predicts long-term mortality

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Background: Thirty-day readmission after percutaneous coronary intervention (PCI) is associated with higher mortality. However, little is known regarding the potential prognostic factor of hospital readmission beyond 30 days. We hypothesized that readmission within 1 year after PCI may also have prognostic significance.
Methods: A total of 746 consecutive patients were discharged alive after PCI for any reason between 2007 and 2011, and were followed-up during a mean of 27.2±0.5 months (maximum 56 months). Of them, 389 patients (52%) were readmitted for any cause, 223 (29.9%) ≤1 year after discharge (<1yGroup). The remaining patients were used as reference group (RefGroup: no readmission or readmission >1 year after discharge). Only first readmission was taken into account. Survival was assessed by Kaplan Meier curves and log-Rank test for group comparison. Multivariable analysis was performed with a proportional-hazards Cox model.
Results: From the 223 patients, 139 (62.6%) were readmitted for cardiovascular causes, 109 (49.1%) for chest pain and 18.9% for a major adverse cardiovascular event (death, myocardial infarction, stroke, revascularization). Almost one half, 97 (43.5%), underwent repeated catheterization (61% new PCI). Patients in the <1yGroup had higher risk characteristics (higher age, creatinine level, number of diseased vessels, and need for hemodynamic support; also lower left ventricular ejection fraction and baseline haemoglobin) than the RefGroup.
There were 34 deaths (15.8%) in the <1yGroup compared to 18 (3.4%) in the RefGroup (p<0.001). Only one third of deaths were from cardiovascular causes, with no differences between groups (35.3% vs. 38.9%; p=0.8). Mean survival from all-cause death was 48.2±1 months in the <1yGroup compared to 52.8±0.4 months in the RefGroup; p<0.001. Mean time to death was 27 months in the overall population, and it was shorter in the <1yGroup (25.6 vs. 27.9 months; p=0.033).
The unadjusted HR for mortality of the <1yGroup patients was 4.58 (95%CI 2.5 –

8.1). In multivariable analysis, readmission during the first year after PCI remained as a mortality predictor [adjusted HR 3.02 (95%CI 1.6 – 5.6)], independently of other relevant clinical and procedural variables.
Conclusions: In an unselected population, nearly one third of the patients undergoing PCI needed to be readmitted during the first year after discharge. Readmission within 1 year identifies a high-risk subgroup of patients and it was associated with a higher mortality risk. Most deaths occurred 2 or more years after discharge and had non-cardiovascular causes.

P5460 | BEDSIDE
Prevalence and outcomes of transradial vs transfemoral percutaneous coronary intervention in a high volume center

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Background and purpose: Radial access reduces major bleeding complications and improves survival of STEMI undergoing primary percutaneous coronary intervention as compared to femoral approach. Our aim was to compare transradial (TR) versus transfemoral (TF) approaches in a non-selected cohort of patients undergoing percutaneous coronary intervention (PCI). We evaluated mortality and MACE at one-year follow-up. The clinical and angiographic data of 4672 consecutive patients treated who underwent PCI between 2007 and 2012 were evaluated retrospectively.
Results: Over the past 5-years, the use of TR in all-comers increased from 86% to 89%. PCI were performed using the TR in 88% of patients. There were no significant differences according to age (65±12,5 vs 66±12,5 p=0,08) or body mass index (27±13 vs 26±5, p=0,62) between TR and TF groups. Female gender (29% vs 21%, p<0,001), cardiogenic shock (11 vs 2%, p<0,001), cardiac arrest (6% vs 2%, p<0,001), prior coronary artery bypass surgery (16% vs 7%, p<0,001), dialysis (6% vs 2%, p<0,001) were the most frequent reasons for using TF.
One year followed up was obtained in 97.9%. The rate of MACE was higher in TF versus TR (20,3% vs 10,2%, p<0,0001) and cardiovascular mortality was increased by three-fold (15.1% vs 5,5%, p<0,001). Target lesion revascularisation did not differ according to the vascular access site approach (6,5% vs 6,1%, p=0,78). In multivariate analysis, TRI was associated with a lower adjusted risk of cardiovascular mortality (Odds Ratio OR: 0.654; 95% CI: 0.46 to 0.922; p=0.0154).
Conclusions: In our center, which has been using radial access in PCI as default strategy for more than 10 years, the use of radial access for PCI continues to increase slightly. The radial approach was associated with a reduced one year cardiovascular mortality and MACE outlining a persisting selection bias and was associated with a similar target lesion revascularisation.

P5461 | BEDSIDE
Predictive value of LDL-C/HDL-C ratio on newly developed cardiac ischemia in patients with previous percutaneous coronary intervention beyond the early restenosis

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Purpose: LDL-C/HDL-C (L/H) ratio is considered as a sensitive risk factor for ischemic heart diseases, however, there is little information regarding the predictive value on newly developed cardiac ischemia in patients with previous percutaneous coronary intervention (PCI) after stabilization. We investigated predictive value of L/H ratio for secondary prevention.
Methods: We examined characteristics of 269 patients with previous PCI who underwent coronary angiography from January 2007 to December 2013 following recurrent cardiac ischemia beyond the early restenosis.
Results: Overall, during median follow-up period of 5.4 years, 61% patients underwent any late revascularization, and 28% and 47% underwent late target lesion revascularization and new lesion revascularization, respectively. Age, diabetes mellitus, T-chol, LDL-C, HDL-C, non-HDL, L/H ratio and HbA1c were detected as predictors of any late revascularization by univariate Cox proportional hazards analysis. Multivariate analysis identified that L/H ratio (HR, 1.32; p<0.001) and HbA1c (HR, 1.13; p=0.017) were independent predictors. Based on the median value of L/H ratio, subjects were classified into high and low L/H ratio groups. Kaplan-Meier estimation revealed significantly higher incidence of late revascularization in high L/H ratio group than in low L/H ratio group in patients with LDL-C ≥100 mg/dl (median L/H ratio, 2.64; p=0.017). However, in patients who could achieve LDL-C <100mg/dl (median L/H ratio, 1.93), difference between the two groups was not significant (p=0.224), and predictor of late revascularization was only diabetes mellitus.
Conclusions: L/H ratio was an important predictor of newly developed cardiac ischemia in patients with previous PCI after stabilization, particularly, in patients with LDL-C ≥100 mg/dl.

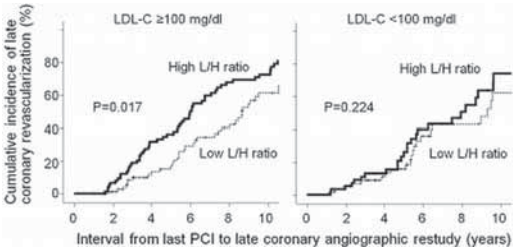

Figure 1. Incidence of late revascularization.

P5462 | BEDSIDE
The leipzig prospective drug-eluting balloon registry: outcome of 484 consecutive patients undergoing PCI using paclitaxel-coated balloons for in-stent-restenosis and de-novo lesions

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Background: Paclitaxel-coated balloon angioplasty (DEB) has emerged as a potential treatment strategy in patients presenting with in-stent restenosis (ISR). However, data regarding mid- and long-term clinical outcome are still lacking. We aimed to evaluate the mid- and long-term safety of DEB- angioplasty in a population-based all-comers setting and investigate predictors of target lesion revascularization (TLR).
Methods: Consecutive patients undergoing DEB-angioplasty were enrolled in this prospective registry. The primary objective was clinically-driven TLR. Secondary objectives were peri-procedural complications and the occurrence of MACE (composite of cardiac death, myocardial infarction, clinically-driven TLR, stentthrombosis, stroke) at 12 months and in long-term follow-up.
Results: Between 4/2009 and 10/2013 484 patients aged 68.4±10.4 years (77.9% male) were enrolled. At 12 months, the rate of TLR was 6.7%. The overall incidence of TLR was 8.3%., 9.2% for BMS-ISR, 10.2% for DES-ISR and 1.3% for de-novo lesions, respectively. We noted no differences in TLR rates in egard to BMS restenosis or DES restenosis. The rate of TLR was significantly higher in patients undergoing DEB for ISR compared to de-novo lesion (P=0.012). Multivariable modelling emerged ISR in coronary artery bypass graft (CABG) as an independent predictor for TLR (P=0.001) as well as the occurrence of MACE (P=0.031).Coronary 3-vessel disease was been shown to be an independent predictors of MACE in Cox regression analysis (P=0.010). The all-cause mortality rate was 7.2% (35 patients, cardiac death 2.9%) after a mean time of 1.73±1.18 years. The secondary objective of MACE at 12 months occurred in 52 patients (14.6%).
Conclusion: The present large, single-centre registry demonstrates a low rate of TLR in long-term follow-up. Therefore, DEB is safe and an effective and promising treatment option especially in patients with de-novo lesions with reasonable clinical outcome.
However, the current study clearly demonstrates ISR in CABG as an independent predictor of TLR and MACE in our multivariable Cox regression analysis. This finding might be partially due by the limited number of patients with ISR in coronary artery bypass graft included in this registry. However, to date no representative data exist reporting the incidence of TLR in the subgroup of patients undergoing DEB for ISR in CABG. Therefore, more clinical studies are of need investigating the clinical outcome of patients after DEB for ISR in CABG in a randomized fashion.

P5463 | BEDSIDE
Prognostic value of chronotropic response in exercise treadmill test after coronary revascularization

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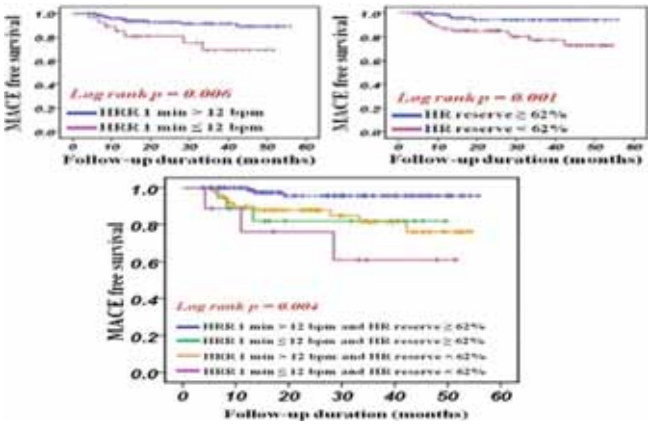
Purposes: Cardiovascular events have been reported at about 10% even though successful revascularization in patients with coronary artery disease. Reduced heart rate (HR) responses to exercise have been reported as independent predictor of cardiovascular events. The aim of this study was to access HR responses to exercise in the prediction of the major adverse cardiovascular events (MACE) in patients with revascularization.
Methods: We retrospectively analyzed 190 patients with successful revascularization and exercise treadmill test (ETT) 4 months later in asymptomatic status. The HR responses in ETT were compared according to the presence of the MACE (cardiac death, nonfatal myocardial infarction and revascularization). HR reserve was calculated as (peak HR - baseline HR) x 100 / (220 - age - baseline HR). Impaired HR reserve was defined as achievement of <80% in patients without beta-blockers (BB) and <62% in patients with BB. HR recovery at 1 minute (HRR 1 min) was calculated as peak HR – HR at recovery 1 minute. Impaired HRR 1 min was defined as a decrease of ≤12 bpm.
Results: The mean follow-up duration was 33.7±13.1 months. There was no difference of demographic, clinical and echocardiographic parameters between both groups. HR reserve was significantly lower in MACE group. In multivariate analysis, HR reserve and HRR 1 min were independent predictors for the MACE. The odds ratios (OR) for the MACE in impaired HR reserve was 5.5 without adjustment, and 6.1 with adjustment. Moreover, the OR for the MACE in patients with

both impaired HRR 1min and impaired HR reserve was 9.6 without adjustment, and 9.4 with adjustment.



MACE according to the HR response

Conclusions: HR reserve in ETT could be a useful predictor for the MACE in the asymptomatic patients with successful revascularization.

P5464 | BEDSIDE
Differences in modes of dual antiplatelet therapy (DAPT) cessation in the United States (US) v Europe: patterns of non-adherence to antiplatelet regimens in stented patients (PARIS) registry substudy

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Purpose: The mode of DAPT cessation has been shown to impact differently on PCI outcomes. We sought to compare modes of DAPT cessation in patients undergoing PCI with stenting in the US vs Europe (EU).
Methods: The PARIS registry was a multicenter, prospective, observational study of patients who had PCI with stent implantation 2009 to 2010. Any cessation in DAPT following PCI was classified by an independent clinical events committee into 3 modes which included discontinuation (physician-deemed DAPT no longer needed), interruption (<14 days for surgery), or disruption (due to bleeding or non-compliance). We compared modes of DAPT cessation and outcomes at 2 year follow up in US vs EU patients.
Results: US patients (n=3660, 73%) were more often obese, more likely to have comorbidities and prior MI, to be smokers, to present with an acute coronary syndrome and to receive bare metal stents whereas EU patients (n=1358, 27%) received longer stents and were more likely to have government/insurance subsidized medication. While EU patients had a greater rate of DAPT discontinuation, mainly after the first year (31.7% vs 65.6%), US patients had more interruption (13.8% vs 1.5%) and disruption (17.8% vs 5.1%) of DAPT at 2 years (Figure). US patients had higher unadjusted rates of death (5.5% vs 2.8%, p<0.001), MACE (7.7% vs 3.5%, p<0.001) and bleeding (8.9% vs 6.8%, p=0.02) compared to EU patients. After multivariate adjustment, MACE remained consistent with crude rates.
Conclusion: EU patients had greater rates of discontinuation whereas interruption and disruption were more frequent in the US. The differences in DAPT cessation modes may be attributable to baseline comorbidities, health insurance coverage, intercurrent adverse events or variability in PCI practice patterns between the US and EU.

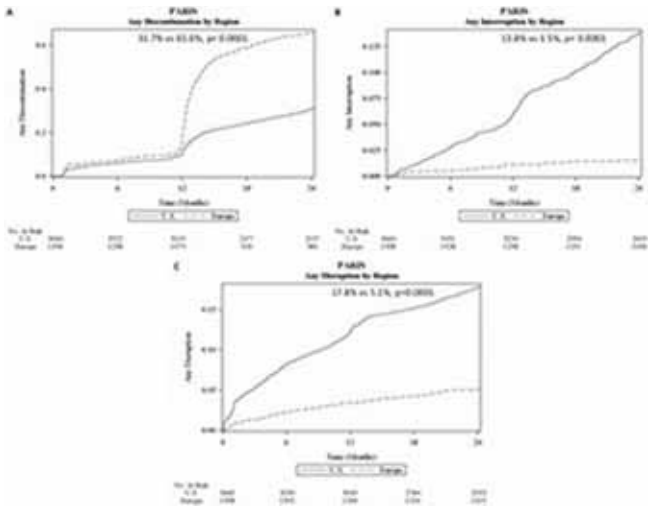

Figure 1. Modes of DAPT cessation at 2 years of follow-up in in Europe vs US. A. Discontinuation (recommended, physician-directed cessation of DAPT because patient is assumed to no longer require DAPT). B. Interruption (temporary i.e. <14 days, of DAPT cessation due to surgical needs). C. Disruption (DAPT withdrawal due to bleeding or non-compliance).

P5465 | BEDSIDE
Risk stratification of stable patients undergoing fractional flow reserve guided percutaneous revascularization and multiple biomarkers assessment

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Purpose: Fractional Flow Reserve (FFR)–guided percutaneous revascularization (PCR) along with optimal medical therapy improves clinical outcome by targeting ischemia-inducing stenosis. Yet, plaque progression or stent failure may cause recurring cardiac events. We assessed the potential impact of inflammatory biomarkers, known to be associated with plaque progression or stent failure, on clinical outcome of patients undergoing FFR-guided PCR.
Methods: We prospectively enrolled 193 stable angina patients (pts) with intermediate coronary stenosis at angiography (i.e. with diameter stenosis 40-70%) undergoing FFR-guided PCR and: i.e. PCR in case of stenosis with FFR≤0.80, deferral in case of stenosis with FFR>0.80. Serum levels of C-Reactive Protein (CRP), a sensitive marker of inflammation, and of Eosinophilic Cationic Protein (ECP), a sensitive marker of eosinophils activation, were assessed the day before FFR-guided PCR. Rate of major adverse cardiovascular events (MACE) as a composite of cardiovascular death, recurring myocardial infarction and PCR was evaluated.
Results: PCR was performed in 78 pts (46%) with FFR≤0.80 (mean age 69±10 years, male 73%) and deferred in 91 pts (54%) with FFR>0.80 (mean age 64±11 years, male 53%). Average clinical follow-up was 31.2±11.5 months. Within the deferred group, CRP levels were significantly associated with higher MACE rate (H.R. [95%C.I.]: 1.04 [1.01-1.07], p=0.015) and pts with MACE [n=8 (9%)] had significantly higher CRP levels than those without (15 [6.5-31.9] vs. 1.6 [0.9-2.9] mg/L, p<0.001). Within the PCR group, ECP levels were significantly associated with higher MACE rate (H.R. [95%C.I.]: 1.05 [1.01-1.09], p=0.021) and pts with MACE [n=14 (18%)] had significantly higher ECP levels than those without (14.4 [9.3-19.5] vs. 4.9 [2.8-10.9] mg/L, p<0.001).
Conclusions: Assessing inflammatory biomarkers allows identification of patients remaining at higher risk of MACEs after FFR-guided PCR.

P5466 | BEDSIDE
Dual antiplatelet therapy over six months increases the risk of bleeding after biodegradable polymer- coated sirolimus eluting stents implantation: insights from the CREATE study

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Background: The optimal duration of dual antiplatelet therapy (DAPT) after drug eluting stent (DES) implantation remains a controversy. The aim of the present study was to evaluate the impact of different DAPT duration on bleeding events between 6 to 12 months after biodegradable polymer coated DES implantation and to determine the predictors and prognostic implications of bleeding.
Methods: This study is a post hoc analysis of the CREATE study population. A total of 2040 patients survived at 6 months were enrolled, including 1639 (80.3%) received 6-month DAPT and 401 (19.7%) received DAPT >6 months. Bleeding events were defined according to the bleeding academic research consortium (BARC) definition and were classified as major/minor (BARC 2-5) and minimal (BARC 1). A left censored method with a landmark at 6 months was used to determine the incidence, predictors and the impact of bleeding on clinical prognosis between 6 and 12 months.
Results: At one year follow up, patient received prolonged DAPT of >6 months had significantly higher incidence of overall (3.0% vs. 5.5%, P=0.021) and major/minor bleeding (1.1% vs. 2.5%, P=0.050) compared with the counterparts who received 6-month DAPT. Multivariate analysis showed that elderly (OR=1.882, 95% CI: 1.109-3.193, P=0.019), diabetes (OR=1.735, 95% CI: 1.020-2.952, P=0.042), history of coronary heart disease (OR=2.163, 95% CI: 1.097-4.266, P=0.026) and duration of DAPT >6 months (OR=1.814, 95% CI: 1.064-3.091, P=0.029) were independent predictors of bleeding. Patients suffered from bleeding events had significantly higher incidence of death (7.0% vs. 0.4%, P<0.001), myocardial infarction (1.4% vs. 0.0%, P=0.035), target lesion revascularization (11.3% vs. 0.7%, P<0.001) and stent thrombosis (4.2% vs. 0.0%, P<0.001).

Conclusions: Prolonged DAPT (>6 months) after biodegradable polymer coated DES increases the risk of bleeding, which is associated with adverse cardiac events at 1-year follow-up.

PCI LONG-TERM OUTCOME

P5468 | BEDSIDE
The clinical impact of borderline peripheral artery disease in patients undergoing percutaneous coronary intervention

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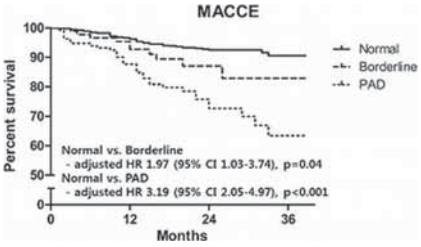
Background: Peripheral artery disease (PAD) is related to increased cardiovascular and cerebrovascular risk after percutaneous coronary intervention (PCI). However, there are little studies to investigate the impact of borderline ABI on clinical outcomes in patients who underwent PCI. This study aims to evaluate clinical implications of borderline PAD patients who underwent PCI.
Methods: A total 1,291 patients who underwent PCI and ankle-brachial index (ABI) between September 2009 and August 2012 were enrolled. Borderline ABI was defined as 0.91 to 0.99 of ABI. The primary outcome was the composite of all-cause death, cerebrovascular event, myocardial infarction or any revascularization (MACCEs).
Results: The median follow-up duration was 570 days (interquartile range 381 to 780). The patients with normal ABI was 1,065 (82%), borderline 89 (7%), and PAD 137 (11%). Cox proportional-hazard analysis showed that the incidence of MACCEs in borderline ABI patients (12.4% vs. 6.1%, adjusted hazard ratio [HR] 1.91, 95% confidence interval [CI] 1.03-3.74, p=0.04) and PAD patients (25.5% vs. 6.1%, adjusted HR=3.19, 95% CI 2.05-4.97, P<0.001) were significantly higher than in those with normal ABI.

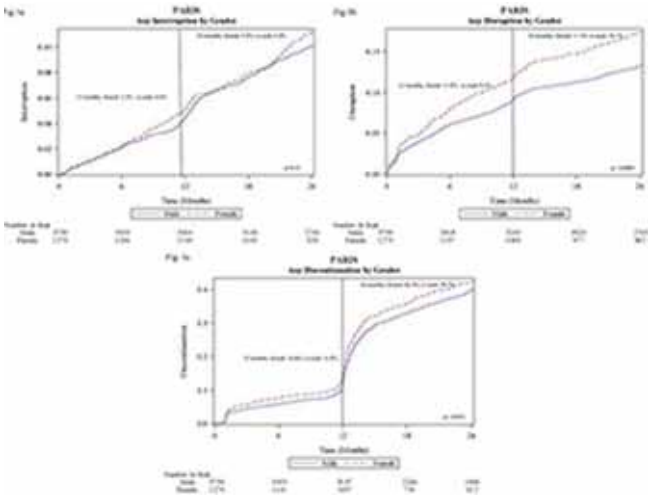


Conclusion: Both borderline ABI and PAD in patients who underwent PCI is significantly associated with increased adverse clinical outcomes compared to those with normal ABI. The risk of adverse clinical outcomes of borderline ABI is lower than PAD.

P5469 | BEDSIDE
Modes of dual antiplatelet therapy (DAPT) cessation in men and women: results from the patterns of non-adherence to antiplatelet regimens in stented patients (PARIS) registry

I. Mastoris[1], S. Sartori[1], J.J. Yu[1], M.W. Krucoff[2], D.J. Cohen[3], D.J. Moliterno[4], G. Dangas[1], A.S. Kini[1], A. Chieffo[5], R. Mehran[1]. *[1]Mount Sinai Medical Center, New York, United States of America; [2]Duke University Medical Center, Durham, United States of America; [3]St. Luke's Mid America Heart Institute, Kansas City, United States of America; [4]University of Kentucky, Lexington, United States of America; [5]San Raffaele Hospital of Milan (IRCCS), Milan, Italy*

Purpose: Previous studies have demonstrated an association between female sex and unfavorable outcomes following PCI. However, the modes of DAPT cessation among women versus men have not been described.
Methods: PARIS was a multicenter, prospective registry of patients prescribed DAPT following PCI for any indication from 2009 to 2010. DAPT cessation included physician-guided discontinuation, interruption (<14 days for surgery) or disruption due to bleeding/non-compliance. We examined baseline characteristics, modes of DAPT cessation and clinical outcomes at 2 years in women (n=1279, 25%) versus men (n=3739, 75%). All events were independently adjudicated.
Results: Women were older, had more comorbidities, and were more likely to be treated with proton pump inhibitors whereas men were more likely to be smokers, have completed a higher level of education, have a history of prior MI or revascularization, and have PCI with longer stents. While there was no difference in DAPT interruption between women and men, women were significantly more likely to have DAPT disruption, and showed a trend toward increased DAPT discontinuation (Figure). Women, had higher rates of death (6.5% vs 4.1% p=0.0005), MACE (7.8% vs 6.1% p=0.03) and bleeding (11.9% vs 7.1% p<0.0001) at 2 years. The impact of DAPT cessation on ischemic events was similar between men and women (pint >0.05).
Conclusion: Compared with men, women had higher rates of DAPT discontinuation and disruption. Although adverse events were more common among women, the impact of DAPT cessation on risk after PCI is non-differential by gender.



Abstract P5469 – Figure 1. Modes of DAPT cessation women vs men. (a) Interruption (temporary DAPT cessation due to surgical necessity with reinstitution of DAPT within 14 days); (b) Disruption (cessation of DAPT due to bleeding or non-compliance); and (c) Discontinuation (recommended, physician-directed withdrawal of DAPT for patient considered no longer require DAPT).

P5470 | BEDSIDE
Efficacy of oral rapamycin plus bare metal stents vs drug eluting stents in the treatment of de-novo coronary artery lesions in the elderly. A five years post-hoc sub-analysis of ORAR 3 trial

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Purpose: ORAR III was a randomized comparison between drug eluting stents (DES) and Oral rapamycin (OR) plus bare metal stent (BMS) implantation, one, three and five years results were reported elsewhere. Presently we sought to assess long term results of the elderly patients (pts) included in the trial.
Methods: From 200 pts included in ORAR III trial between august 2006 and september 2007 in Buenos Aires, Argentina, we selected all elderly pts (≥65 yrs), 40 in the OR plus BMS and 48 in DES group. OR was given as a bolus of 10 mg the day before the index procedure followed by 3 mg per day for the following thirteen days. All pts received first generation C-mark approved stents. Primary endpoint was to compare in hospital, follow up and overall costs (US dollars) at one, three and five years. Secondary end points included death (D) of any cause, acute myocardial infarction (MI) and stroke (S) and were analyzed as major adverse cardiovascular events (MACCE) and Target Vessel Failure (TVF), as the composite of cardiac death, MI and target vessel revascularization (TVR).
Results: Dyslipemia (p=0.01) was the only significantly different clinical or demographic baseline variable in this subgroup. At five years of follow-up, death of any cause was similar for both groups (10.0% OR vs 22.9% DES, p=0.1), the composite of D, MI or S was better with OR than DES (10.0% vs. 29.2%, p=0.02), and TVF was 25.0% vs. 43.8% in OR vs DES, respectively (p=0.06). Costs (US$) were significantly lower at hospital (4782.9±859.4 vs. 6632.3±1733.8 p≤0.001), follow up (1029.7±2630.6 vs. 2913.3±3534.1, p=0.007) and overall (5812.7±2636.1 vs. 9545.6±4659.1, p≤0.001) for OR vs DES respectively.

Table 1. 5 years clinical outcome and cost

	OR (n=40)	DES (n=48)	P value
Death, MI and stroke %	10.0	22.9	0.1
Target vessel failure %	25.0	43.8	0.06
Hospital costs (US$)	4844.1±21.5	6693.5±36.1	<0.001
Follow up costs (US$)	1006.9±66.5	4081.3±80.1	<0.001
5 years costs (US$)	5851.1±66.6	10774.8±100.7	<0.001

Conclusions: In this long term sub-analysis from the randomized ORAR III study, OR is cost saving in the treatment of de novo coronary lesions and appears to improve outcome at 5 years in this elderly cohort of pts.

P5471 | BEDSIDE
Factors influencing clinical decision making for cessation of dual antiplatelet therapy within 1 year among patients undergoing PCI with drug eluting stents: results from the PARIS registry

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Purpose: Current guidelines recommend 6-12 months of dual antiplatelet therapy (DAPT) after PCI with drug eluting stents (DES). We sought to identify baseline factors that influence clinical decision-making for DAPT cessation within 12 months.
Methods: We performed a post-hoc analysis of the PARIS registry (n=5018), of whom 4,134 patients underwent PCI with DES. We compared baseline demographic, clinical and procedural characteristics between patients continuing DAPT beyond 12 months and patients with DAPT cessation within one year. Independent correlates of early DAPT cessation were identified using logistic regression.
Results: Compared to patients continuing DAPT beyond 1 year (n=3431, 83%) patients with any cessation within the first 12 months (n=703, 17%) were older, more often female, American and more likely to be discharge on warfarin with a lower prevalence of dyslipidemia and family history of coronary artery disease. These associations persisted after multivariable adjustment (Table) and were similar after excluding patients with adverse events in the first year. Presentation with an acute coronary syndrome and procedural parameters, such as stent length and vessel were not associated with DAPT duration.

Predictors of early DAPT cessation

	OR [CI%]	P-value
Age, per year	1.02 [1.01–1.02]	0.0001
Female gender	1.23 [1.02–1.48]	0.034
Region (USA vs. Europe)	1.54 [1.25–1.89]	<0.0001
Dyslipidemia	0.73 [0.59–0.89]	0.002
Family History of CAD	0.83 [0.68–1.00]	0.046
Previous CABG	0.78 [0.61–1.01]	0.06
Concurrent warfarin use	4.84 [3.58–6.55]	<0.0001

CAD: coronary artery disease; CABG: coronary artery-bypass grafting; DAPT: dual anti-platelet therapy.

Conclusion: Baseline clinical and demographic factors, rather than presentation or procedural parameters, are independent correlates of early DAPT cessation within 12 months. Table: Factors independently associated with DAPT cessation within 12 months

P5472 | BEDSIDE
Impact of stent fracture after sirolimus-eluting stent implantation on 8-year clinical outcomes

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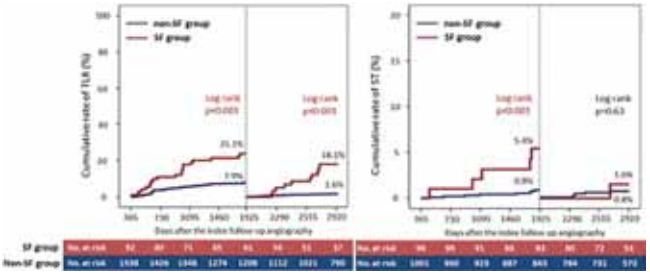
Purpose: This study aimed to assess the impact of stent fracture (SF) after SES (sirolimus-eluting stent) implantation on 8-year clinical outcomes.
Methods: From 2002 to 2005, 1795 lesions (1119 patients) were treated exclusively with SES, in which follow-up angiography was performed within one year after index procedure. Excluding 165 lesions underwent target lesion revascularization (TLR) and 19 patients developed stent thrombosis (ST) within one year after SES implantation, 1630 lesions (1100 patients) constituted the study population. SF was defined as the separation of stent segments or stent struts at follow-up angiography. We defined the clinical endpoint as all-cause death, cardiac death, myocardial infarction (MI), definite ST, and TLR. TLR was evaluated on a per-lesion basis, whereas the other clinical endpoints were on a per-patient basis. Clinical endpoint rates were calculated by the Kaplan-Meier methods and compared by the log-rank test.
Results: SF was observed in 92 lesions (5.6%). The median follow-up duration was 2975 days. The cumulative rates of MI, definite ST, and TLR were significantly higher in the SF group (10.2% versus 4.1%, p=0.01; 6.9% versus 1.7%, p=0.001; and 38.7% versus 9.4%, p<0.001). On the other hand, those of all-cause death and cardiac death didn't significantly differ between the 2 groups (23.9% versus 27.6%, p=0.23 and 4.9% versus 8.6%, p=0.13). As the figure showed, those of TLR, both from 1 to 5 years and beyond 5 years, were also significantly higher in the SF group. That of definite ST from 1 to 5 years was significantly higher in the SF group, whereas that beyond 5 years showed no difference between 2 groups.
Conclusions: SF after SES implantation was associated with higher cardiac adverse events not only from 1 to 5 years, but beyond 5 years.



Kaplan-Meier curves for TLR and ST.

P5473 | BEDSIDE
Impact of Mehran contrast-induced nephropathy risk score for the prediction of clinical outcomes after percutaneous coronary intervention

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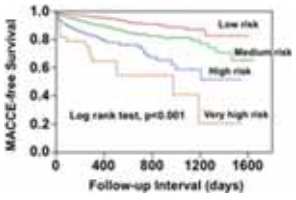
The Mehran Risk Score (MRS) has been demonstrated to be clinically useful for prediction of contrast-induced nephropathy (CIN) after percutaneous coronary intervention (PCI). We aim to investigate the association with MRS and clinical outcomes in patients who underwent PCI.
Methods: Study subjects consisted of 2198 consecutive patients treated with PCI from ICAS (Ibaraki Cardiovascular Assessment Study) multi-center registry, except for the patients who were receiving hemodialysis and died within seven days (n=34). We categorized them into 4 groups according to MRS (low-risk: ≤5, medium-risk: 6-10, high-risk: 11-16 and very high-risk: 16<). We evaluated contrast-induced nephropathy (CIN) and major adverse cardio-cerebral accidents (MACCE), which were defined as all-cause death, myocardial infarction (MI), congestive heart failure, or cerebro-vascular accidents (CVA).
Results: A total of 192 patients (8.7%) developed MACCE. At multivariate analysis, MACCE in very high-risk group was more than 5-fold higher (HR 5.40, 95% CI: 2.96-9.28, p<0.001) when compared with low-risk group and was also increased in high-risk group (HR 3.72, CI: 2.59-5.32, p<0.001) and medium-risk group (HR 1.97, CI: 1.45-2.69, p<0.001). Kaplan-Meier analysis showed that increasing risk for MACCE was seen across the increasing MRS groups (p<0.001) (Figure). The odds ratio for CIN was 4.09 (95% CI: 1.72-9.17, p=0.002) in the very high-risk group, 1.49 (95% CI: 0.89-2.42, p=0.120) in the high-risk group, and 1.08 (95% CI, 0.74-1.54, p=0.693) in the medium-risk group, as compared with the low-risk group.



Conclusions: MRS might be potentially useful information for a prediction of CIN and clinical outcomes after PCI.

P5474 | BEDSIDE
A nationwide study on prognosis after percutaneous coronary intervention in persons with and without familial myocardial infarction

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Purpose: A family history of coronary artery disease is an independent risk factor for incident cardiovascular disease, and familial forms of cardiovascular disease can occur up to a decade before sporadic forms. However, it is unknown whether the prognosis after myocardial infarction (MI) in persons with a family history of MI differs from the post-MI prognosis in persons without such family history.
Methods: We linked data from national Danish registers and created a cohort of persons undergoing first-time percutaneous coronary intervention (PCI) without any prior revascularization in the period 2000-2010. We then identified the parents and siblings of all cohort members and determined whether these relatives had been registered with an MI before the cohort member's PCI; based on this determination, we classified the PCI-cohort members as having or not having a family history of MI. We followed our cohort for re-PCI, CABG and death (all-cause mortality). Using Cox-regression with age at PCI as the underlying timescale, we estimated hazard ratios (HRs) for re-admission for a second PCI or a first cardiac bypass surgery (CABG) after PCI, and mortality ratios, by history of MI in a parent or sibling. All estimates were adjusted for previous or co-existing co-morbidities, sex, age at PCI in strata, calendar period and number of relatives.

Results: We included 63,077 persons with first-time PCI in the cohort, of whom 5,675 had a history of MI in a parent or sibling. We followed our cohort members for up to 10 years, with an average follow-up of 3.8 years, and found a 10% increased risk of second PCI or first CABG in those with a family history of MI, compared to those with no family history. There was no association between family history of MI and all-cause mortality, regardless of whether we looked at the whole cohort or stratified by sex (of either relative or cohort member), age of relative at MI, and age of cohort member at PCI.
Conclusions: Family history of MI appeared to have a modest impact on the post-MI prognosis as measured by re-admission for second PCI or CABG and mortality, which suggests that once coronary artery disease has developed, the familial forms have a almost as good a prognosis as the non-familial forms.

P5475 | BEDSIDE
Relative survival and excess mortality following unprotected left main stem percutaneous coronary intervention 2005-2010: Analysis of 5065 cases from the British Cardiac Intervention Society (BCIS)

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Purpose: To estimate long term relative survival (RS) and excess mortality rates (EMR) following unprotected left main stem (UPLMS) PCI for ST-elevation myocardial infarction (STEMI), non ST-elevation acute coronary syndrome (NSTEACS) and chronic stable angina (CSA) in the national PCI registry (British Cardiac Intervention Society, BCIS) from 2005 to 2010.
Methods: Of 5,065 UPLMS PCI cases across 89 hospitals, RS was estimated (Ederer II method) as the ratio of observed to expected survival in a disease-free population, stratified by age, sex and calendar year. EMRs were derived using Poisson regression as a function of follow-up time and standardized for sex, age and biennial year of PCI.
Results: Table 1 describes the characteristics of the UPLMS PCI cohort. For STEMI, RS was lower (0 years vs. 6 years; 61.3% vs. 56.3%) compared with NSTEACS (83.0% vs. 74.2%) and CSA (96.7% vs. 92.3%) (Fig.1). Compared with CSA, EMRs were higher in STEMI (13.6, 95%CI 9.8-18.8) than NSTEACS (4.6, 95%CI 3.3-6.4). Age over 75 years for NSTEACS but not STEMI or CSA significantly increased EMRs (1.5, 95%CI 1.2-1.9). Sex and biennial year of PCI did not impact on EMRs.

Table 1. Demographic characteristics

	STEMI N=704 (15.0%)	NSTEACS N=2233 (47.4%)	CSA N=1771 (37.6%)
Mean (SD) age, years	67.4 (13.7)	72.2 (12.3)	68.9 (11.4)
Male (%)	515 (73.2)	1481 (66.3)	1277 (72.1)

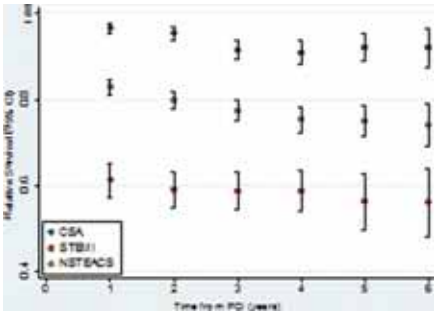

Figure 1. Long term-relative survival.

Conclusion: Long-term RS after UPLMS PCI estimates were greatest for CSA compared with NSTEACS and STEMI. Only for NSTEACS was age a risk factor for long term excess mortality.

P5476 | BEDSIDE
Long-term prognosis in chronic total occlusions (CTO): a retrospective comparison of successful revascularization with non-successful intervention or primary medical therapy

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Interventional revascularization of coronary chronic total occlusions (CTO) represents a challenging field in cardiology with limited success and patency rates. Data on long-term prognosis after successful revascularization are conflicting and the impact of non-successful intervention or primary medical strategy on prognosis and quality of life (QoL) remains unclear.
Methods: 796 patients (pt) treated for CTO at our institution from 2006 to 2009 were contacted to evaluate the rate of major adverse cardiac and cerebrovascular events (MACCE) and to assess QoL using telephone follow-up visits and validated questionnaires at a mean follow-up of 2.5±1.1 years.
Results: Complete follow-up data including SF-36 Health Survey and Seattle Angina Questionaires could be obtained from 249 pt (age 67±11 years, female 22%, coronary 3-vessel-disease 53%, LV-EF 51±14%). 80 pt (32%) had successful interventional revascularization for the CTO-vessel (Group A). 53 pt (21%) had a non-successful intervention (Group B), whereas 116 pt (47%) had been primarily advised for medical treatment (Group C). Pt in Group A were younger than in Group C (64±10 and 69±10 years, respectively; $p<0.01$) and less likely to have a smoking history than in Group B ($p<0.02$). Groups did not differ in terms of other cardiovascular risk factors nor with respect to CTO vessel. Death from any cause occurred in 15.1% and 12.9% in Group B and C, respectively, but only in 3.8% in Group A ($p<0.02$). A trend towards longer MACCE-free survival was observed for Group A. Pt in Group A had been initially highly symptomatic (52.6% with Angina CCS Class III or IV compared to 20.8% in Group B and 21.5% in Group C; $p<0.001$) and symptoms improved significantly until follow-up ($p<0.001$), compared to stable angina levels in the other groups (B: p=0.546, C: p=0.07). QoL assessment showed a significant benefit for Group A with respect to physical activity and symptoms of pain.
Multivariate analysis revealed a benefit for Group A compared to Group C regarding the combined endpoint of death/ non-fatal myocardial infarction/hospitalisation for angina pectoris (HR 0.574 (0.362-0.911), $p<0.02$). Independent predictors for MACCE were high-grade heart failure symptoms, low LV function and age.
Conclusion: A successful intervention for CTO decreases MACCE rate and increases health-associated QoL. Especially older and highly symptomatic pt or with impaired LV function should be offered an interventional attempt for CTO revascularization. An unsuccessful attempt seems not to have a negative impact on prognosis compared to conservative medical treatment.

P5477 | SPOTLIGHT
New insights on acute expansion and longitudinal elongation of bioresorbable vascular scaffolds in-vivo and at bench test

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Purpose: To evaluate the acute BVS-vessel interactions (i.e., expansion patterns and longitudinal integrity) using optical coherence tomography (OCT).
Methods: Consecutive patients who underwent de novo PCI with a single BVS implantation/lesion, followed by OCT assessment were included. The predicted area (derived from the predicted diameter) according to the deployment pressure provided in the compliance chart was compared with actual area in all analyzed cross-sections. Qualitative plaque assessment was performed by dividing each cross-section into 4 quadrants, with each quadrant being labeled according to its most prevalent plaque component, as follows: normal, fibrous, calcified, and lipid plaque. Cross-sections were divided in tertiles of expansion (Actual Area/Predicted Area: <70%, 70%-80%, and >80%) and plaque components were quantified and compared among the tertiles. Bench test was also performed.
Results: A total of 28 patients (31 BVS) were included and 663 cross-sections were analyzed. The presence of calcified plaque was significantly more common in the lowest (9.7%) compared with the mid (8.8%) and highest (6.3%) tertiles of scaffold expansion ($p<0.01$, respectively). Conversely, a progressive increase in the percentage of lipid (i.e., soft) plaque was revealed in lowest (8.9%), mid (14%), and highest (17.1%) tertiles of expansion (p=0.229 and p=0.445, respectively). Seventeen (54.8%) scaffolds were elongated (i.e., actual length longer than the predicted length) and no BVS constriction was revealed. Mean elongation percentage was 8.0%. Higher rates of calcified plaque (13.4±21.1% vs. 2.5±4.4%, p=0.309) and lower percentage of lipid plaques (6.7±8.0% vs. 21.3±23.5%, p=0.250) were identified in the elongated scaffolds. Mean actual area/predicted area of the elongated scaffolds was significantly lower compared with the non-elongated scaffolds (74.3±12.9% vs. 77.4±11.9%, $p<0.01$). No adverse events were observed among these two groups. We hypothesized that the polymer, which is softer and has higher conformability than metallic alloys, when submitted to high deployment pressures while in contact with hard (calcified) plaques, could stretch longitudinally, leading to elongation; indeed, we were able to reproduce the elongation phenomenon in vitro by dilating a scaffold with high pressure (16 atm) in a hard tube: an 18mm scaffold was elongated to 19.1mm.
Conclusions: From the analysis of real-world population, 1. Compliance chart information is unreliable to optimize BVS PCI results, 2. Calcified plaques may impair adequate BVS expansion, and 3. BVS may elongate after deployment.

P5478 | BEDSIDE
Six-month clinical outcomes after implantation of an everolimus-eluting bioresorbable scaffold or an everolimus-eluting metallic stent in complex lesions: a propensity matched comparison

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Objectives: Bioresorbable scaffold is a novel approach that provides transient

vessel support with drug delivery capability without the long-term limitations of metallic drug-eluting stents. The everolimus-eluting bioresorbable scaffold has been shown to be effective in the context of first-in-man trials including simple lesion(s). However, the effect of ABSORB implantation in more complex lesions cannot be directly extrapolated from these findings. We sought to evaluate the impact of this novel technology on the intermediate- term clinical outcomes in a real-life population with complex lesions in comparison with the propensity matched population treated with everolimus-eluting metallic stents.
Methods: Since September 1st 2012, our institution commenced the use of ABSORB scaffold in patients with complex lesions including a long lesion (>32mm in length), a calcified lesion, a bifurcation lesion and a large vessel with up to 4mm in diameter. Patients presenting with stable angina, unstable angina and non-ST elevation myocardial infarction were included. In total, 187 consecutive patients treated exclusively with Absorb scaffold(s) before July 2013 were included in this analysis. From our institutional all-comer X-SEARCH registry, 372 patients exclusively treated with EES were selected by propensity-score matching. Six-month clinical results are collected regarding occurrence of scaffold/stent thrombosis and major adverse cardiac events (MACE), defined as a composite of all-cause mortality, myocardial infarction (MI) or target vessel revascularization (TVR).
Results: The baseline characteristics were similar between the two groups. In the ABSORB group, 368 scaffolds were implanted in 187 patients, with a procedural success rate of 98.1%. The treated lesions were on average 26.63 mm in length, including 72 bifurcations, 131 calcified lesions and 37 chronic total occlusions. At 6 months, survival status was available in 96.9%. The all-cause mortality was similar between the groups (ABSORB: 2.2% vs. EES 2.1%). The 6-month data on the occurrence of MI, repeat revascularization and stent/scaffold thrombosis are currently being adjudicated.
Conclusion: The intermediate-term safety and efficacy of the ABSORB scaffold in complex lesions in comparison with its metallic counterpart will be presented at the meeting.

P5479 | BEDSIDE
Optimal inflation time depends on stent length in a novel prolonged inflation protocol

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Introduction: We devised a novel stent inflation protocol which requires pressure stability (<0.3 atmosphere drop) for at least 30 seconds at full balloon expansion for stent deployment to be considered optimal. We have shown using OCT that this method produces less stent malapposition and greater stent expansion compared to a rapid inflation–deflation protocol. The goal of the present study is to determine whether any patient, lesion, or stent characteristic is associated with prolonged inflation duration and the safety of such prolonged inflation times.
Methods: We analyzed 530 stent implants (112 bare metal and 418 drug eluting stents) in 375 patients with native coronary disease.Multivariate analysis was performed to identify predictors of prolonged stent inflation.
Results: Patient characteristics were as follows: age 64±9 yr; mean BMI 30.2±5; diabetes 39%; chronic kidney disease 11.5%; acute coronary syndrome 29%; stent diameter 2.8±0.4 mm; stent length 17±6 mm; inflation pressure 16±2atm.Mean stent inflation time was 101±36 sec[range 30-241 sec]. On multivariable analysis,stent length was the only factor significantly associated with prolonged stent inflation (Table 1). Inflation time was significantly prolonged in stents more than 20mm in length compared to stents less than 20 mm long (111.8±42 vs 97.8±34 sec, p=0.03). Prolonged inflation was prematurely terminated in 13 implantations (2.4%; severe chest pain and/or ST elevation =9, hypotension=2,unknown=2). In-hospital events occurred in 23 patients (6.1%, periprocedural MI=18, acute stent thrombosis=5).

Table 1. Multivariate analysis of relationship between various factors and prolonged stent inflation

Variable	Age	BMI	Diabetes	CKD	Calcification	Stent diameter	Stent length
p value	0.44	0.18	0.09	0.7	0.45	0.94	0.03

BMI: body mass index; CKD: chronic kidney disease.

Conclusion: In a large series, stent optimal stent implantation requires approximately 1.5 min with stent length being the only factor related to required time. Prolonged stent inflation does not appear to increase the risk of periprocedural complications. We recommend that rather than relying on angiographic balloon expansion or an arbitrary pre-determined inflation time, a stable inflation pressure for at least 30 sec should be the goal to achieve optimal stent expansion. This hypothesis is being further tested in a prospective randomized study (NCT01952873).

CHEST PAIN ASSESSMENT IN THE EMERGENCY DEPARTMENT

P5481 | BEDSIDE
Validation of the GRACE freedom from events score in an emergency department chest pain population

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Purpose: Risk stratification of patients with chest pain/ acute coronary syndrome (ACS) is an important component of assessment and a driver of decision-making. The GRACE Freedom-from-Event score (GFFES) was developed to identify patients with a low risk of adverse in-hospital events. Our aim was to validate this score in an emergency department (ED) chest pain cohort.
Methods: Prospective observational cohort of adult patients attending a community teaching hospital ED and assessed for potential ACS. Defined major adverse cardiac events (MACE) were death, new MI, cardiac arrest or other life-threatening arrhythmia, high degree atrioventricular block, cardiogenic shock or new atrial fibrillation (AF) within 30 days of the index visit. The primary outcome of interest was the predictive performance of the GFFES for MACE by clinical performance and ROC analysis.
Results: 1076 patients were studied. There were 14 MACE (1.3%, 95% CI 0.8-2.2%). 721 patients (67%) were classified as low risk by the score (GFFES score ≥287). There was 1 MACE in the low risk group; a 40 year-old with new AF in the week following index presentation but no ACS. Sensitivity of GFFES for MACE was 92.9% (95% CI 64.2-99.6%), specificity 67.8% (95% CI 64.9-70.6%) and negative predictive value (NPV) 99.9% (95% CI 99.1-100%). Area under the ROC curve was 0.80 (95% CI 0.72-0.89). For the cohort assessed and then discharged from ED, sensitivity was 100% (46.3-100%) with NPV of 100% (99.2-100%).
Conclusion: In this large single site prospective validation study in ED chest pain patients, GFFES showed good discrimination, sensitivity and negative predictive value. It may be a useful tool for assigning patients to appropriate levels of care based on risk.

P5482 | BEDSIDE
Head to head comparison of risk stratification scores HEART vs TIMI score for patients with undifferentiated chest pain and correlating with frequencies of in-hospital major adverse cardiac events

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Purpose: Risk stratification of undifferentiated chest pain patients admitted to chest pain assessment unite (CPAU) according to HEART and TIMI risk score and correlating with in-hospital frequencies of major adverse cardiac events-MACE (Troponin positive MI, revascularisation percutaneouns coronary intervention-PCI or coronary artery bypass grafting-CABG) and death.
Methods and material: Retrospective observational study. 1022 patients were admitted to chest pain assessment unite during study period from February 2011 to March 2013. 109 patients were excluded from study. Out of 109 patients excluded 4 patients went back to home country, 7 patients left against medical advice, 10 patients were diagnosed with pericarditis and 89 patients had too limited data to evaluate leaving a study group of 913. In a study group of 913 consecutive patients admitted with undifferentiated chest pain to (CPAU) were risk stratified according HEART and TIMI score. The patients were then divided in Low, Intermediate and high risk categories depending on their HEART score (0-3 low-risk, 4-6 Intermediate-risk, and 7-10 high-risk) and TIMI score (0-2 Low-risk, 3-4 Intermediate-risk, 5-7 high-risk). The frequencies of in-hospital adverse outcomes (MACE) were then compared in each risk category between HEART and TMI scores.
Results: Troponin positive MI were noted in 1.5%, 10.2% and 72.2%; PCI in 1.7%, 12.2% and 36.1%; and CABG 0%, 2% and 0% in Low, Intermediate and High HEART risk score. In TIMI risk group troponin positive MI was noted in 4.5%, 17.5 and 75.5%, PCI in 5.9%, 15.9% and 25.0%; and CABG 0.48%, 1.9% and 2.5% respectively. Frequencies of admission outcomes significantly correlated well with HEART and TIMI risk score (p<0.001).
Conclusion: HEART and TIMI risk score correlate well with frequencies of in-hospital adverse out comes (MACE) in term of troponin positive MI, PCI and CABG, however HEART risk score is found better in excluding MACE than TIMI risk score in Low and Intermediate category but comparable for predicting MACE in high risk group.

P5483 | BEDSIDE
Impact of the clinical introduction of high-sensitivity cardiac troponin T assay on rates of coronary angiographies and exercise stress tests in acute chest pain - Insights from an international trial

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Purpose: With the clinical introduction of more sensitive cardiac troponin (cTn) assays, concerns about potential higher rates of false positives leading to an increased number of clinically not indicated coronary angiographies and exercise

stress tests arose. On the other hand, the increased sensitivity potentially improves the early rule out of acute myocardial infarction (AMI), decreasing the need for further stress tests.
Methods: We conducted a prospective, international diagnostic study to compare the incidence of coronary angiographies and exercise stress tests before and after the introduction of Roche high-sensitivity (hs) cTnT assay, replacing a less sensitive, conventional cTnT assay. A total of 2631 consecutive patients presenting with symptoms suggestive of AMI to the emergency department (ED) of three hospitals were included. Coronary angiographies and cardiac stress tests were only considered for this analysis if they were performed during the index visit or within the following three months.
Results: During the first phase using a conventional cTnT assay, 26% (387 out of 1513) of all patients underwent coronary angiography as compared to 25% (284 out of 1118) patients after the introduction of the hs-cTnT assay (p=0.919 for comparison). The percentage of angiographic findings showing normal vessels (10% before vs. 7% after the introduction of hs-cTnT, p=0.431) or just mild coronary sclerosis (4% vs. 6%, respectively) did not differ significantly between the two phases (p=0.431). Cardiac stress tests were markedly less frequent after the introduction of the hs-cTnT-assay (28% vs. 19%, respectively, p<0.001). Median time spent on the ED until discharge could be reduced significantly for out-patients after the introduction of hs-cTnT (359 minutes before vs. 277 minutes after hs-cTnT, p<0.001).
Conclusions: As compared to times using a conventional, less sensitive cTnT assay, the introduction of a hs-cTnT assay does neither result in higher rates of coronary angiographies nor in an increased number of normal or just mild angiographic findings among patients presenting with acute chest pain to the ED. However, the use of hs-cTnT reduces the median length of stay on the and seems to substantially improve the early rule-out of AMI by nearly halving the rates of subsequent exercise stress tests.

P5484 | BEDSIDE
Is high sensitivity troponin T a useful marker for ACS in advanced renal insufficiency?

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Purpose: Renal insufficiency (RI) is a well known limiting factor in the evaluation of myocardial infarction (MI) with troponin T (TnT). Less data are available for high sensitivity-TnT (HsTnT), in particular it is unknown in which amount the stage of RI influences HsTn level in the diagnostic workout for diagnosis of Acute Coronary Syndromes (ACS).
Methods: We evaluated 533 pts coming to the emergency department for chest pain or symptoms suggestive of ACS. 449 were discharged without diagnosis of ACS and 84 with a diagnosis of ACS. In all pts we analized the HsTnT level at the admission and at 3-6 hours; we consider positive a first measurement ≥14 ng/L and a relative delta ≥20 or 50% at the second sample, based on the admission level, according to literature. The population was classified according to the glomerular filtration rate (GFR) level: GFR ≥60 ml/min, GFR <60 >30 ml/min, GFR <30 ml/min. We assessed the area under the curve (AUC) value by categorical values.
Results: 87 out of 533 pts had GFR<60 ml/min, among these pts 65 (75%) had HsTnT ≥14 ng/L at first sample and 20 (31%) had diagnosis of ACS. HsTnT at first sample had low diagnostic accuracy with increasing stage of RI, in particular in the group with GFR <30 ml/min (AUC 0.54). In these pts the use of relative delta led to an increase in AUC value from 0.54 to 0.85. The improvement was smaller and not significant in the other two groups.
Conclusions: Our study demonstrates that HsTnT levels have a poor early performance in case of advanced RI but, in these pts, the use of an appropriate relative delta may increase diagnostic accuracy for ACS.

P5485 | BEDSIDE
Mechanical complications of acute myocardial infarction in the modern era of reperfusion: type, incidence, associated factors and prognosis

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Introduction: The incidence of mechanical complications following acute myocardial infarction (AMI) has fallen with the provision of reperfusion therapies. Although, they remain life-threatening and need prompt detection and management. In the acute phase, they include ventricular septal rupture (VSR), free wall rupture (FWR) and acute mitral regurgitation (AMR).
Objective: To describe the type, incidence, associated factors and prognosis of AMI mechanical complications in the modern era of reperfusion.
Methods and results: Retrospective observational study including 1969 consecutive patients admitted in a Coronary Unit for the period of 4 years, since 2009, with the diagnosis of AMI (mean age 64 years, 77.2% male). The minimum follow-up performed was 6 months. The incidence of mechanical complications was 1.0% (n=20): 3 VSR, 12 FWR and 5 AMR. Patients with mechanical complications were older (75 vs. 64 years, p<0.001). At admission, they presented mainly with ST elevation AMI (90% vs. 49%, p=0.001) and had higher incidence of heart failure (50.0% vs. 21.3%, p=0.002), shock (20.0% vs. 2.6%, p<0.001) and renal failure (65% vs. 27%, p<0.001). NT-proBNP value (6962 vs. 2885 pg/mL, p=0.004) and the risk scores GRACE (197 vs. 144, p<0.001) and Crusade (51 vs. 29, p=0.011) were higher. Time since symptom onset until reperfusion with primary angioplasty was superior in patients with mechanical complications (7h54min vs. 4h54min, p=0.006) as was more frequent the absence of effective reperfusion after primary angioplasty (30.8% vs. 8.7%, p=0.006). During hospitalization, these patients had higher peak creatinine (1.7 vs. 1.2 mg/dL, p=0.002) and more rhythm disturbances, as new onset atrial fibrillation (25.0% vs. 9.4%, p=0.019) and high degree atrioventricular block (20.0% vs. 5.6%, p=0.006). These patients were submitted to more aggressive therapies, as the use of amines (40.0% vs. 6.7%, p<0.001), ventilation support (29.4% vs. 5.5%, p<0.001) or intra-aortic balloon pump (40% vs. 2.6%, p<0.001). The prognosis was unfavorable at short and long term (mortality during hospitalization of 40% vs. 3.7% and during follow-up of 41.7% vs. 5.2%; p<0.001). According to mechanical complication type, the prognosis was better in AMR (global mortality of 20%) and worst in VSR and FWR (global mortality of 66.7% and 83.3%, respectively).
Conclusion: The definition of a clinical profile related to mechanical complications, including variables as shock at admission, ischemia time or reperfusion success might be important to develop strategies to monitor more closely these patients.

P5486 | BEDSIDE
High sensitivity troponin T in managing patients with suspected acute coronary syndrome: comparison between two diagnostic algorithms

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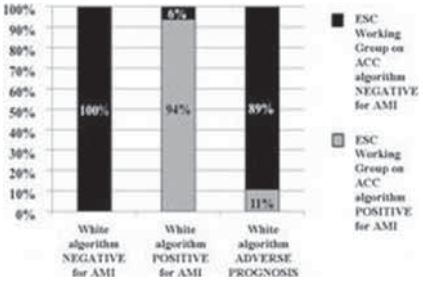
Background: The universal definition of acute myocardial infarction (AMI) requires a rising/falling pattern of cardiac troponin with at least one value above the 99th percentile, but the actual Δ change between the serial measurements of troponin levels has not been defined yet. Herein we compared the algorithm published by White (WA) and that proposed by the European Society of Cardiology Working Group on Acute Cardiac Care (ESC-WG-ACC-A).
Methods: We enrolled 251 consecutive patients admitted to Emergency Department for suspected acute coronary syndrome (ACS) and for whom high-sensitivity Troponin T (hs-TnT) levels were determined in serial blood samples. We divided the study population into 3 subgroups according to the WA (positive for AMI, negative for AMI, adverse prognosis) and then we analyzed how the diagnosis changed according to ESC-WG-ACC-A within each of them.
Results: A final diagnosis of AMI was made in 38 patients (15%) according to the WA, while unstable angina was diagnosed in 11% of cases.
Among patients with hs-TnT curve positive for AMI according to the WA, we observed a difference in 6% of cases by using the ESC-WG-ACC-A (figure). In particular, the latter did not confirm AMI in those patients who had a falling pattern in troponin levels.
Moreover, when hs-TnT was ≥14ng/L (99th percentile) without a positive curve for AMI (the so-called Adverse Prognosis subgoup according to the WA), the ESC-WG-ACC-A was discordant in 11% of cases. In these patients the final diagnosis was different from ACS in almost all cases (93%), meaning that ESC-WG-ACC-A would have diagnosed AMI in a larger number of patients.



Comparison between Hs-TnT algorithms.

Conclusions: The WA seems to be more specific in distinguishing patients with real AMI diagnosis from those with elevated troponin levels for reasons other than AMI.

P5487 | BEDSIDE
Optimal cutoff-value of siemens cardiac troponin I ultra assay in patients with kidney disease for the early diagnosis of acute myocardial infarction

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Purpose: The recent introduction of more sensitive cardiac troponin (cTn) as-

says improved the early diagnosis of acute myocardial infarction (AMI). However, its diagnostic utility has never been tested in patients with kidney disease (KD), who are known to have elevated levels of cTn already in the absence of AMI, which may lead to a lower diagnostic value of more sensitive cTn in this high-risk subgroup.
Methods: We conducted an international multicenter study to examine the diagnostic accuracy of the Siemens cTnI Ultra assay in 2695 consecutive patients presenting to the emergency department with symptoms suggestive of AMI, of whom 419 (16%) were determined to have KD (MDRD GFR <60ml/min/1.73m^2) and to derive the optimal cutoff value for the diagnosis of AMI in patients with KD. The diagnostic accuracy was further compared to a conventional, less sensitive cTn assay (Roche Troponin T fourth generation). The final diagnosis was adjudicated by two independent cardiologists based on hs-cTnT.
Results: AMI was the final diagnosis in 36% (n=150) of all KD-patients as compared to 18% in patients with normal kidney function (p<0.001). Among KD-patients with other diagnoses than AMI, baseline cTnI-levels were elevated above the 99thpercentile in 19%, In patients with KD the diagnostic accuracy at presentation, quantified by the area under the receiver-operator-characteristic curve (AUC), was significantly greater for Siemens cTnI as compared to the standard cTnT assay (AUC for cTnI, 0.87 vs. AUC for the standard assay, 0.82, p=0.02). In patients presenting within three hours after the onset of chest pain, the superiority of Siemens cTnI Ultra over conventional cTnT was even more pronounced (AUC 0.86 vs. 0.72, p=0.006). In KD, the optimal cTnI cutoff derived from the ROC curve was 46 ng/l compared to 19 ng/l in patients with normal kidney function (standard 99th percentile 40 ng/l, provided by the manufacturer).
Conclusions: The investigates sensitive cTnI assay has a very high diagnostic accuracy also in KD-patients and is superior to a conventional cTnT-assay. Mild elevations are common in non-AMI patients. The optimal cutoff-level in KD-patients seems to be around the 99th percentile of a standard population, whereas the optimal cutoff-level in patients with normal kidney function tends to be only half of the suggested cutoff-value. ClinicalTrials.gov number, NCT00470587

P5488 | BEDSIDE
Clinical presentation and outcome of patients with false-positive ST-segment elevation myocardial infarction

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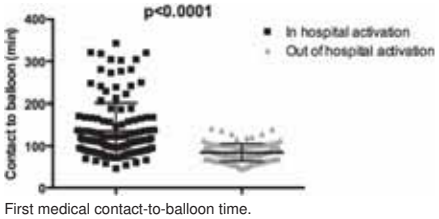
Background: Activation of cardiac catheterization laboratory through regional code STEMI programs by paramedics shortens treatment time but may increase the rate of false-positive STEMI.
Methods: In this case-control study, 259 consecutive patients with true code STEMI were compared to 81 consecutive patients with false-positive code STEMI activation. The clinical presentation, electrocardiographic features, etiology, and outcomes were assessed. We also compared the effectiveness of out of hospital and in-hospital activation of code STEMIs.
Results: The false-positive and true STEMI groups were similar in their coronary artery disease risk factors except for dyslipidemia (28.4% vs. 42.5%, P=0.02). Patients with false-positive STEMI were less likely to have typical chest pain (43% vs. 79%, P<0.01). The morphology of the ST elevations in the false-positive STEMI group showed more concave ST elevation (60% vs. 31%, P<0.01), and less reciprocal ST-depression (16% vs. 70%, P<0.01). The false-positive STEMI group had higher rate of ventilator support requirement (12.3% vs. 5.4%, P=0.03) and 30-day mortality (9.9% vs. 6.9%, P=0.02). 60% of the true STEMIs activated by paramedics achieved the 90 minutes first medical contact-to-balloon target compared to only 23% of the in-hospital activations (Figure).



First medical contact-to-balloon time.

Conclusions: Patients with false-positive code STEMI may have relatively poor outcome due to other medical conditions. Careful history and review of ECG may help differentiate this group from true STEMI.

P5489 | BEDSIDE
Circumflex-related acute coronary syndrome: how to make an early diagnosis?

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Purpose: This investigation points out the role of resting echocardiography in an Emergency Department (ED) as tool for the early diagnosis of left circumflex artery (LCx)-related acute coronary syndrome (ACS).
Methods: 451 (322 males) patients (pts) were observed in a cardiologist-run Chest Pain Unit because of a typical/atypical chest pain, negative ECG, normal T troponin, normal LV wall-motion (WM) by echo at admission. Time of monitoring: 11±6 h. Monitoring protocol:12 leads-ECG telemetry monitoring; high sensitivity T troponin at time 0,4,8 h; resting echocardiogram at admission; chest X-ray; stress test before discharge. To achieve the aim of the investigation we added an echo-monitoring of LV regional WM at time 2,4,8 hours from admission.
Results: We found 63 ACS (13,9%).The initial mode of ACS detection was: 1)LV Regional WM echo abnormalities (23 pts, 36,5%); 2)ECG (ST-T) modifications (28 pts, 44,4%);3) T-Trop elevation (12 pts, 19%). In the ACS echo-detection GROUP (23 pts), the culprit coronary lesion was on LCx in 15 pts (65,2%), on LAD in 5 pts (21,7%) and on RCA in 3 pts (13%);(LCx vs RCA=p<0.001;LCx vs LAD=p<0.01). In other words, 15 out of 23 pts with normal ECG and T-Trop at presentation and echo-detection of ACS had a LCx-culprit lesion. In ACS echo-detection GROUP+culprit lesion on LCx (15 pts), the ECG remained NORMAL during hospitalization period in 11 patients (73,3%), compared to LAD-culprit lesion pts (0%) and RCA-culprit lesion pts (0%);(LCx vs LAD=p<0.001;LCx vs RCA=p<0.001).
Conclusions: The ACS due to a culprit coronary lesion on the LCx may have a characteristic pattern defined by high percentage of: 1)normal ECG; 2)LV wall motion abnormalities detected by resting echocardiography. Echocardiography could become an essential tool used to diagnose the LCx-related ACS.

P5490 | BEDSIDE
Diagnostic performance of hsTnT and POCT-TnT for the diagnosis of AMI in clinical routine

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Introduction: NSTEMI is defined as a rise or fall of cardiac troponin with at least one value above the 99th percentile of a healthy reference population. The cut-off value used is recommended to have a coefficient of variation of less than 10%. POC-systems do usually not meet these criteria at the 99th percentile. In this analysis, the diagnostic performance of a POC-test for TnT is compared with a hs-TnT test performed in the hospital laboratory.
Methods: All patients with routine TnT-testing in the ED were enrolled in two time-frames of 3 and 4 months. Double TnT-measurements were performed with a contemporary sensitive assay in EDTA whole blood on the AQT-90 (Radiometer) and a hs-TnT assay in heparin plasma on the Cobas-602 (Roche analytical systems). Only admission values of non-trauma patients were analyzed. The diagnostic performance for AMI was compared at two cut-offs for each TnT-test, the 99%tile and the "conventional" threshold: hsTnT at 14ng/L and 50ng/L and AQT-TnT at 16ng/L and 30ng/L. Endpoint was the hospital main diagnoses at discharge.
Results: Of all 3.396 patients, 7.9% had a final diagnosis of UAP (267), 3.7% NSTEMI (124) and 0.9% STEMI (32). A coronary angiography was performed in 11.5% (389) and PCI was required in 46.5% of these patients (181). The diagnostic performance of the respective TnT-assays is shown in table 1.

Table 1. Diagnostic performance of hsTnT and AQT-TnT at the 99th percentile and at the "conventional" threshold

	hsTnT		AQT_TnT	
	14ng/L	50ng/L	16ng/L	30ng/L
Sensitivity	91.67	66.67	81.41	71.79
Specificity	66.79	93.27	85.37	93.06
PPV	11.73	32.30	21.13	33.23
NPV	99.40	98.31	98.96	98.56
Accuracy	67.93	92.05	85.19	92.08

Conclusions: In our cohort the diagnostic performance of conventional POC-testing was comparable to hsTnT. HsTnT in clinical routine provides information about slightly elevated Tn-values which might be of added value for further diagnostic evaluation. The implementation of a 99th percentile cut-off is accompanied by a major decrease in specificity, PPV and overall accuracy while NPV only increases slightly, thus questioning the routine clinical benefit.

P5491 | BEDSIDE
Prognostic role of copeptin in non-ST-elevation acute coronary syndrome

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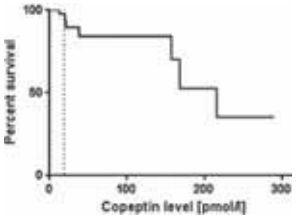
Purpose: The aim of the study is to investigate if copeptin provides additive information to hs-troponin in the prediction of outcome in patients with symptoms of non-STE ACS and non-conclusive ECG.
Methods: Consecutive patients with suspected ACS, chest pain lasting less than 6 hours, and non-conclusive ECG were enrolled in this prospective study. Copeptin was blindly measured at presentation. N-terminal pro-brain natriuretic

peptide (NT-proBNP) and hs-troponin levels were measured. GRACE risk score was assessed at admission. Final diagnosis was set by two independent cardiologists based on current guidelines and available data. Copeptin was regarded as positive when >18.9pmol/l. Patients were evaluated after 6 months.
Results: In the cohort of 153 patients, there were 108 NSTEMI (70.6%), 28 UA (18.3%), 17 other causes of chest pain (11.1%). Median copeptin serum level was higher in NSTEMI than in UA and other patients (14.2; 7.9; 7.8 pmol/l; respectively, p=0.007).
In the follow-up, copeptin was significantly correlated with GRACE score (p=0.0006; r=0.27) and with mortality at 6 months [OR=40,8; CI (2.28-732), p=0.0002] (figure). Levels of copeptin were higher in patients who died than in survivors (38.9 vs. 11.2 pmol/l, p=0.0014) while there was no difference in troponin levels (200.0 vs. 103.4 ng/ml, p=ns). Significant correlation of copeptin with NT-proBNP (p=0.0023; r=0.25) was aggravated by a tendency towards higher copeptin levels in patient with heart failure (NYHA>1) at 6 month (p=0.06).



Conclusions: In a population of patients admitted to emergency department with chest pain and non-conclusive ECG copeptin is a valuable predictor of long-term prognosis of mortality. Therefore copeptin can be regarded as a co-efficient marker in the management of patients with non-STE ACS.

P5492 | BEDSIDE
Diagnosis of acute myocardial infarction in patients with complete left bundle branch block: prospective evaluation of the Sgarbossa criteria

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Purpose: Patients with suspected acute myocardial infarction (AMI) and complete left bundle branch block (LBBB) in the ECG present a unique diagnostic challenge to clinicians. The Sgarbossa criteria were established to identify patients with AMI with acute coronary occlusion, but have not been validated in unselected patients with acute chest pain after the introduction of the universal definition of AMI. This was the aim of our study.
Methods: We included 2938 unselected patients presenting with acute chest pain to the emergency department in a prospective multicentre diagnostic study. Patients with complete LBBB at presentation were included in this subgroup analysis. The ECGs were reviewed by two independent cardiologists blinded to the adjudicated diagnosis for the presence or absence of the Sgarbossa criteria. The final diagnosis of AMI was adjudicated by two independent cardiologists according to the universal definition of AMI using all information becoming available during the work-up including coronary angiography, echocardiography and serial high-sensitivity cardiac troponin T testing.
Results: 83 patients (2.8%) had a complete LBBB at presentation, of whom AMI was the adjudicated diagnosis in 32 patients (39%). Applying the Sgarbossa criteria only four patients (12,5% of all patients with LBBB and AMI) could be correctly identified as having an AMI. 28 patients with AMI were missed (sensitivity 13%, negative predictive value 65%). There were no falsely positive results with the Sgarbossa criteria, therefore both specificity and positive predictive value were 100%.
Conclusion: The Sgarbossa criteria are highly specific for AMI according to the universal definition, but have a very low sensitivity. Absence of the Sgarbossa criteria should not be misinterpreted as absence of AMI in patients presenting with acute chest pain. Our findings may help to better manage patients with complete LBBB in the future.

ACUTE CORONARY SYNDROME – PATHWAY CHALLENGES

P5494 | SPOTLIGHT
The ECG transmission, teleconsultation and direct transport system reduces hospital mortality of STEMI patients referred to a distant interventional cardiology center

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Objective: To evaluate the impact of ECG teletransmission, teleconsultation and direct transport bypassing local hospitals without the possibility of invasive AMI treatment, for hospital mortality in patients with STEMI, referred to a distant intervention cardiology center (ICC).
Methods: 1411 consecutive patients who were admitted to ICC from December 2001 to April 2011, with enzymatically confirmed STEMI, were studied. Only patients from outside the ICC catchment area (average distance to ICC - 64 km) were included. Up to October 2005, patients were admitted under a two-stage strategy (2-T; pick-up address - the nearest noninvasive hospital - ICC), and since November 2005 - a one-stage strategy (1-T; pick-up address - ECG teletransmission and teleconsultation - ICC). In both groups, hospital mortality and the factors affecting it were analyzed. The statistical analyzes used Pearson chi-square test and U Mann-Whitney test. Statistical significance was considered for $p<0.05$.
Results: 2-T group consisted of 657 and 1-T group - 754 patients. Between the two groups no statistically significant differences in terms of gender, age, and diabetes were showed. In the 2-T group more often noninvasive treatment were performed (9.4 vs 4.4%, $p<0.001$). Hospital mortality in the 2-T group was 11.4% in the 1-T group - 7.7% (relative risk reduction - RRR 32.3%, 95% CI, 7.8-51.6, p=0.013). Hospital mortality was significantly reduced in subgroup of patients aged ≥65 years (18.6 vs 10.9%, RRR 41.4%, 95% CI 16.2-59.1, p=0.003), women (18.2 vs 10.6%, RRR 41.9%, 95% CI, 4.1-64.8, p=0.031), patients with diabetes (53.5%, 95% CI, 4.4-77.3, p=0.032) and women aged ≥65 years (22.1 vs 11.9%, RRR 46.0%, 95% CI, 7.6-68.5, p=0.022). In the 2-T group factors that significantly increased hospital mortality were: age ≥65 years ($p<0.001$), female gender (p=0.003), diabetes (p=0.034) and noninvasive treatment (p=0.003) in 1-T group only age ≥65 years (p=0.001).
Conclusions: The introduction of tele-ECG and replace the two-stage transportation to a distant ICC by direct transportation, was associated with a reduction in hospital mortality in STEMI.

P5495 | BEDSIDE
Mode of presentation of patients with ST-segment elevation myocardial infarction in Singapore and its impact on door-to-balloon time and clinical outcome

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Purpose: In the management of patients with ST-segment elevation myocardial infarction (STEMI), the timeliness of reperfusion via primary percutaneous coronary intervention (PPCI) is important in determining the morbidity and mortality. The timeliness of PPCI is estimated by the door-to-balloon (D2B) time which has become a key performance measure. Current guidelines recommend a D2B of <90 minutes. Given that most STEMIs occur out of hospital, the mode of presentation, whether by emergency medical service (EMS) or by self-presentation (SP) is an important factor influencing the timeliness of treatment and possibly clinical outcomes.
Methods: From January 2009 to December 2011, 957 patients (86% male, mean age of 58 + 12 years) presented to our hospital for STEMI and underwent PPCI. We evaluated the relationship between the 2 different modes of presentation with median door-to-balloon (D2B) time and in-hospital mortality. Data were collected retrospectively on baseline clinical characteristics, angiographic findings, therapeutic modality and hospital course.
Results: The majority of STEMI patients (64%) utilized EMS with the remaining 36% being SP. The percentage of patients achieving D2B <90 minutes was 84%. The median D2B time was significantly shorter in patients presenting via EMS (57 minutes vs 66 minutes in the SP group, $p<0.0001$). Despite shorter D2B time, the EMS group had a significantly higher in-hospital mortality rate than the SP group (6.4% vs 2.9%, p=0.02).
Patients in the EMS group had a higher incidence of hypertension and hyperlipidemia and were significantly older at presentation. They were more likely to have triple vessel and obstructive left main disease on coronary angiography. The incidence of cardiogenic shock was also significantly higher in the EMS group.
Conclusion: Although the majority of patients utilised EMS and had a significantly shorter D2B time, they paradoxically had a higher rate of in-hospital mortality. Our preliminary data suggested a possible threshold limit to D2B time in which further reduction does not impact mortality in STEMI. Patients with "sicker" features were more likely to use EMS in our study which was associated with increased mortality.

P5496 | BEDSIDE
Clinical characteristics and outcome of STEMI patients with early (3 hours) presentation treated by primary PCI or fibrinolysis therapy

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Background: It is well known that prognosis of ST-segment elevation myocardial infarction (STEMI) patients (pts) is time dependent on applying reperfusion therapy (RT), and that the type of reperfusion has secondary influence especially during first three hours. The choice of type of RT, primary percutaneous coronary intervention (p-PCI) or fibrinolysis (FT) depends on many factors, but in high risk pts p-PCI is more suitable and with better prognosis than FT. In spite of that, in real life, p-PCI is the preferred therapy for low risk patients. There are not enough

data about mortality and the type of applied RT in STEMI patients hospitalized during first three hours in Serbia as transition country.
Results: Data were used from the hospital registry for Acute Coronary Syndrome in Serbia (HORAKS) and observed STEMI pts during three years, from 2007 to 2009, hospitalized in 52 Coronary Care Units. In 15354 consecutive STEMI pts, mean age 63.6±12.0 years, m/f 65/35, RT was done in 8502 (55.4%) pts. The most of reperfused pts, 4986 (58.6%) arrived during first three hours; mean age 59.6±11.4 and more received fibrinolysis (FT) 3277 (65.7%) pts than pPCI 1709 (34.3%) pts. The pts in FT group were older (60.1±11.3 vs 58.7±11.5, p=0.000) than pts in p-PCI group, with higher prevalence of diabetes (20.1%, vs. 17.6%, p=0.004), with higher prevalence of renal failure (4.3% vs. 3.1%, p=0.035) and heart failure (27.9% vs. 18.5%, p=0.000). Doctors decision to choose the p-PCI or FT (HL test, $\chi 2$= 10.421, p=0.237, c -statistic 0.669, SE 0.006, 95% CI 0.657-0.681) was dependent on pts ages <65 years, the time from symptoms onset (>120 minutes), the anterior localization, pts without heart failure, non-diabetes pts, non-previous myocardial infarction and with previous PCI; additional factors were gender, previous CABG, stroke, anemia, ages ≥75 years. The mortality in whole reperfused group of pts was 7.5%; in p-PCI group was 4.3% and FT group was 8.7%. However, the time from symptom onset to hospital arrival was longer in p-PCI group 92.4±36.4min vs. FT group 80.9±37.4min, p=0.000.
Conclusion: The STEMI high risk patients with early (≤3 hours) presentation and possibility for on-time reperfusion were more often reperfused by fibrinolysis, contrary to the current clinical practice guidelines for STEMI, where such patients should be treated with p-PCI in order to better prognosis. In our study, the mortality of these patients was statistically better in p-PCI (4.3%) than in FT (8.7%) group.

P5497 | BEDSIDE
Suspected left bundle branch block equivalent STEMI: analysis in a primary PCI programme

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Background: Patients presenting with suspected acute left bundle branch block ST elevation MI equivalent (aLBBB-STEMI) present a higher risk of a false positive diagnosis and have a wore prognosis when confirmed. The latest North American STEMI guidelines restrict the indication for PPCI for patients with aLBBB-STEMI to those with specific acute ECG features (Sgarbossa criteria). We sought to determine the accuracy of the presenting diagnosis, and the extent to which a high Sgarbossa score correlated with confirmed aLBBB-STEMI in a large cohort of patients presenting to a PPCI centre with acute myocardial infarction (AMI).
Methods: We interrogated the database of a register of all acute coronary syndrome cases presenting to a PPCI tertiary care centre in the southern region of Ireland from 2006 to 2013 inclusively. All cases classified on referral or admission as STEMI with LBBB were identified. The diagnostic ECG was used to confirm the presence of LBBB and the Sgarbossa criteria were applied: ST elevation >1mm in a lead with a positive QRS complex (5 points); ST depression in lead V1, V2 or V3 (3 points); ST elevation >5mm in a lead with a negative QRS complex (2 points). STEMI was diagnosed by angiographically confirmed acute occlusion of an epicardial artery with a significant elevation of cardiac troponin T.
Results: Nearly 1900 cases of STEMI were referred for PPCI in the study period. Thirty eight patients were registered as STEMI with LBBB as a referral or admitting diagnosis. LBBB was confirmed in 79% (30/38). Of the patients with confirmed LBBB, nearly half, 46.7% (14/30) had true STEMI. Twenty percent (6/30) of patients with LBBB had a Sgarbossa score of >3. Of these patients, 83% (5/6) had STEMI, 3 confirmed angiographically, 2 dying before angiography. Fifty seven percent (17/30) of patients with LBBB had a Sgarbossa score of 0. Four of these 17 (24%) patients were diagnosed with STEMI.
Conclusions: True aLBBB-STEMI was found in a very small number of cases presenting for PPCI. Over half of cases referred as aLBBB-STEMI were false positive. An elevated Sgarbossa score was specific in diagnosing aLBBB-STEMI but restricting PPCI only to those with an elevated Sgarbossa score risks missing true aLBBB-STEMI cases. LBBB continues to pose an operational challenge in PPCI protocols and further work is warranted to determine the best approach to these patients.

P5498 | BEDSIDE
Effects of immediate invasive strategy on occurrence of in-hospital bleeding in non-STEMI patients

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Purpose: Current clinical practice guidelines for the management of non-STEMI patients recommend risk stratification and invasive treatment. The purpose of this study was to investigate whether immediate intervention is associated with higher in-hospital bleeding rates.
Methods: We randomized 323 non-STEMI patients into the immediate intervention (<2h after randomization, n=162) and the delayed intervention group (2-72h after randomization, n=161). Patients were excluded in case of hemodynamic instability, heart failure and life-threatening ventricular arrhythmias on admission. Bleeding was defined in accordance with the definitions used in the landmark The Timing of Intervention in acute Coronary Syndrome (TIMACS) trial. Patients not already on antiplatelet therapy received aspirin and clopidogrel according to the current guidelines for management of non-STEMI.
Results: Median time to angiography in the immediate group was 1.3h and 61.5h in the delayed group (p<0.001). Baseline clinical characteristics were similar, except for the higher rate of diabetes in patients undergoing delayed intervention (33% vs. 22%, p=0.024). There was a trend for higher in-hospital bleeding rates in the immediate compared with the delayed intervention group (9.9% vs 4.3%, OR 2.41; 95%CI 0.96-6.02, p=0.06). The observed difference was mainly due to more access-site bleeding in patients undergoing immediate invasive procedure (immediate 8% vs delayed 3.7%). Immediate intervention was associated with a significantly higher rate of minor bleeding (7.4% vs 0.6%, p=0.01). Occurrence of major bleeding was similar in both groups (2.5% vs 3.7%, p=0.59). Blood transfusion was administered in two cases in the delayed and in one case in the immediate intervention group. There was one intracranial bleeding in a patient randomized to the immediate invasive strategy.
Conclusion: Occurrence of in-hospital major bleeding in non-STEMI patients is similar in immediate versus delayed invasive strategy. Immediate intervention is associated with higher rates of minor bleeding events.

P5499 | BEDSIDE
Comparison of transradial versus transfemoral approach for primary PCI in diabetic patients with ST-elevated acute myocardial infarction

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Purpose: The aim of the study is to compare the outcome of transradial access (TRA) vs. transfemoral access (TFA) in primary percutaneous coronary intervention (PPCI) for ST elevation myocardial infarction (STEMI) in diabetic patients. Artery access change towards TRA was observed, as potentially beneficial strategy to improve outcomes of intervention for STEMI patients with diabetes.
Methods: The data of diabetic acute STEMI patients that underwent PPCI were analyzed during transitional access period from default TFA to TRA, within the year of 2007 to 2010. The registry recruited all-comers patients regardless of presentation in acute STEMI. Major bleeding complications, early death rates, and overall MACE rates (composite of death, stroke, re MI and TVR) after 2 years follow-up were compared between TRA and TFA.
Results: There were 364 diabetic patients (age range 43 to 86 years) out of 1808 patients that underwent PPCI in STEMI during that period. Interventions were successfully done in 236 with TRA artery access and 128 with TFA. The 30-days and 1 year mortality rates were lower in TRA compared to TFA (6.4% vs 17.2%, p=0.001, and 8.5% vs 18.8%, p=0.004, respectively). The 30 days and at 2 years follow-up, MACE rates were favorable for TRA vs TFA group (9.7% vs 18.8%, p=0.021 and at F-up 25.4% vs 35.2%, p=0.034 respectively). The major bleeding and non-CABG bleeding rates were more favorable for TRA than TFA (3.4% vs 13.3%, p<0.001, and 1.3% vs 9.4%, p=0.001, respectively). The univariable and stepwise multivariable Cox-regression analysis was performed, adjusted hazard ratio was calculated and adjusted Kaplan Meier curves were created.

N=364	TRA (n=236)	TFA (n=128)	p
MACE 30 d	9.7%	18.8%	0,021
MACE 2 y	25.4%	35.2%	0,034
Death 30 d	6.4%	17.2%	0,001
Death 1 y	8.5%	18.8%	0,004

Conclusion: Transradial access strategy for primary coronary intervention is associated with significant early and two years mortality and MACE rate reduction comparing to transfemoral access strategy for primary coronary interventions in diabetic STEMI patients.

P5500 | BEDSIDE
Spontaneous coronary artery dissection; an uncommon cause of acute coronary syndrome

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Background and aims: Spontaneous coronary artery dissection (SCAD) is a rare cause of acute coronary syndrome more frequently diagnosed in women and sometimes related with peripartum period. The diagnosis is usually made by coronary angiography. Due to its not well-known pathophysiology and low incidence, clinical features, prognostic and treatment of these patients remain unknown. The purpose of the present study was to analyze clinical, angiographical characteristics and prognostic of patients with confirmed SCAD.
Methods: This is a prospective registry of patients with SCAD diagnosed in our centre from October 2009 to January 2014. All patients were diagnosed with coronary angiography and were regularly followed in the outpatient clinic or by telephone contact. In most of the cases a follow-up coronary CT was performed to evaluate coronary artery patency. After initial diagnosis a conservative approach

was mandatory in all cases. Only patients with persistent angina and severe coronary flow disruption were revascularized
Results: Thirty patients with SCAD were recruited (from a total of 3905 acute coronary syndromes). Most of them were female (97%), ST-elevation myocardial infarction was the most frequently observed clinical presentation (53.3%) followed by non ST-elevation infarction and unstable angina. A low prevalence of cardiovascular risk factors was observed: smoking (63.3%), hypertension (17%) and dyslipidemia (17%). Over 17% of the cases were in peripartum period. Eight patients (26.6%) were treated with PCI and only one (3.3%) underwent coronary artery bypass graft. All other patients were treated conservatively. No differences between both groups were found, in part due to the small sample size. Overall mortality rate was 6.6%, one patient that required cardiac TC and one death, both included in revascularized group. Patients in the conservative group presented a low rate of major cardiac events during the follow-up (median 611 days; IQR 852) 13.4% of readmissions, 4.5% reinfartion and only one patient required revascularization after the first episode. Follow-up coronary CT (performed in 53.3% patients) showed no evidence of residual lesion or persistent coronary dissection in 93.7% patients. Coronary aneurism was detected in 12.5%
Conclusions: In our experience SCAD is more frequent in female with low cardiovascular risk factors. Conservative medical treatment was the most common used and seems to be appropriate with an excellent prognostic and good angiographic evolution. PCI should be restricted to cases of persistent angina or compromised coronary flow.

P5501 | BEDSIDE
Long term-prognostic value of multivessel or culprit-only revascularization in patients with ST-elevation myocardial infarction and multivessel coronary disease

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Objective: Many ST-segment elevation myocardial infarction (STEMI) patients have multivessel disease. There is still controversy in treatment strategy in STEMI patients with multivessel disease. We compared clinical outcomes between multivessel revascularization and culprit-only revascularization in this setting.
Methods: We performed a retrospective analysis in 600 patients (67.4±12.7 years; 25.2% female) admitted by STEMI in our department between 2004 and 2012, with multivessel coronary disease underwent percutaneous coronary intervention (PCI). Using Cox proportional hazards regression analysis, we evaluate the long-term prognostic value of complete revascularization.
Results: 42.7% of patients underwent culprit-only PCI. 105 patients (17.5%) died during the follow-up (4.2±2.8 years) and 32 patients presented reinfarction (5.3%). Mutilvessel PCI was not associated with lower rates of mortality (HR 0.81, CI 95% 0.54-1.20, p=0.291; HR) and reinfarction (HR 1.22, CI 95% 0.61-2.46, p=0.575). Stratifying by GRACE risk score groups, we also did not find differences between multivessel revascularization and culprit-only revascularization.
Conclusion: Our findings support the current guidelines recommendation to perform culprit-only PCI in STEMI patients with multivessel coronary artery disease without hemodynamic compromise.

P5502 | BEDSIDE
Impact of multivessel coronary artery disease on reperfusion success in patients with ST-elevation myocardial infarction - insights from cardiac magnetic resonance imaging

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Background: A significant portion of patients with ST-elevation myocardial infarction (STEMI) display multivessel coronary artery disease (MVD). However, data on the association of MVD and reperfusion success are scarce. Thus, we thought to analyse the impact of MVD on infarct size, microvascular obstruction (MO) and myocardial salvage index (MSI) assessed by cardiac magnetic resonance imaging (CMR) in a large unselected cohort of patients with STEMI reperfused by primary percutaneous coronary intervention (PCI).
Methods: STEMI patients reperfused by primary PCI (n=1074) within 12 hours after symptom onset underwent CMR 3 days after the index event (interquartile range [IQR] 2-4). Infarct size and MO were measured 15 min after gadolinium injection. T2-weighted and contrast-enhanced CMR were then used to calculate MSI. Severity of coronary artery disease was graded as single-vessel disease compared to MVD. Further, a detailed set of clinical, angiographic and electrocardiographic parameters was recorded. The primary endpoint was defined as a composite of death, non-fatal myocardial reinfarction and congestive heart failure (MACE). Clinical follow-up was conducted after 12 months.
Results: MVD was present in 48.5% (n=521) of all patients. Patients with MVD were older (66 [IQR 55-73] vs. 60 [IQR 50-70] years, p<0.001) and more often diabetics (26.3 vs. 17.5%, p=0.001) in comparison to those with single-vessel disease. Angiographic reperfusion success defined as TIMI-flow III post-PCI (87.6 vs. 88.1%, p=0.92) and ST-segment resolution (60 [IQR 25;80] vs. 60 [30;80]%, p=0.18) were similar between both groups.
Patients with MVD displayed no significant differences in infarct size (17.5 [IQR 8.4-26.4] vs. 16.0 [IQR 8.5-24.4]%LV, p=0.15) and extent of MO (0.4 [IQR 0.0;1.6] vs. 0.3 [IQR 0.00-1.7]%LV, p=0.71) as well as MSI (52 [IQR 33-74] vs. 53 [IQR 36-72], p=0.48) in comparison to patients with single-vessel disease.
Finally, the presence of MVD was significantly associated with the time-dependent occurrence of MACE (log-rank comparison p=0.004).
Conclusion: MVD is not associated with impaired reperfusion success assessed by CMR. The adverse clinical outcome of patients with MVD might thus rather be explained by more advanced coronary artery disease itself and unfavourable baseline characteristics.

P5503 | BEDSIDE
Feasibility and efficacy of zotarolimus-eluting stent in the patients with acute coronary syndrome: optical coherence tomography analysis

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Background: Drug-eluting stent in the lesions with acute coronary syndrome (ACS) is one of the major predictors of late stent thrombosis. The purpose of this study is to evaluate feasibility and efficacy of zotarolimus-eluting stent (ZES; Resolute-integrity or Endeavor stent) in the ACS lesions, using optical coherence tomography (OCT) in vivo.
Method: OCT was performed at 9-month follow-up in 40 ACS patients treated with ZES (14 Resolute-integrity and 26 Endeavor). Every observed stent struts were analyzed at intervals of 1mm. Neointimal coverage of struts, stent apposition, and neointimal thickness (NIT) were evaluated.
Result: In total, 2737 struts in 14 Resolute-integrity stents and 5576 struts in 26 Endeavor stents were analyzed. Frequencies of exposed struts and of incompletely apposed struts were 3.2±3.5% / stent and 1.2±1.6%/stent in Resolute-integrity stent, 0.5±0.9% / stent and 0.05±0.1%/stent in Endeavor stent (p<0.001, p=0.001, respectively). The mean thickness of neointima was 0.1±0.09 mm and 0.3±0.1mm (p<0.001). Thrombus was not detected in all patients.

OCT analysis

	Resolute	Endeavor	p
Mean number of analyzed struts/stent	195.5±69.0	214.5±69.6	0.42
Frequency of exposed struts/stent (%)	3.2±3.5	0.5±0.9	<0.001
Frequency of incomplete apposed struts /stent (%)	1.2±1.6	0.05±0.1	0.001
Mean neointimal thickness,mm	0.1±0.09	0.3±0.1	<0.001

Conclusion: These data would suggest feasibility and efficacy of ZES in the lesion of ACS. However, stent coverage is better in Endeavor stent than in Resolute-integrity stent in those lesions.

P5504 | BEDSIDE
Higher in-hospital-mortality of NSTEMI as compared to unstable angina despite higher rate of invasive therapy in clinical practice - results of the EHS ACS Registry

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Background: About half of ACS present without ST-segment elevation. Current ESC guidelines for the management of NSTE-ACS recommend risk stratification to decide about the appropriateness of invasive treatment. This risk stratification also includes troponins which define the diagnosis of NSTEMI. Little is known about treatment and outcome differences between NSTEMI unstable angina pectoris (UAP) in clinical practice.
Methods: Between Oct 2006 and Oct 2008, 21,872 consecutive patients with ACS were enrolled into the Euro-Heart-Survey ACS-Registry to document treatment and hospital complications. We examined the differences in treatment and outcome of patients with NSTEMI and UAP in Europe.
Results: A total of 13,018 patients (59.5%) presented with NSTE-ACS, 7,688 (59.1%) had NSTEMI, 5,330 (40.9%) had UAP. NSTEMI patients were older and more often suffered from diabetes, peripheral artery disease and renal failure. They were more likely to undergo an invasive strategy with early PCI as compared to patients with UAP. Despite the more aggressive treatment, NSTEMI had

	NSTEMI (n=7688)	UA (n=5330)	p-value
Age (years)	70.9	66.8	<0.01
Female gender	64.9%	61.3%	<0.01
Prior MI	28.6%	31.5%	<0.01
Prior PCI	15.5%	21.0%	<0.01
Cardiogenic shock	1.9%	0.3%	<0.01
Coronary angiography	66.2%	51.4%	<0.01
Early PCI	48.3%	34.7%	<0.01
Death	4.8%	1.1%	<0.01
MI	1.7%	0.9%	<0.01

a significantly higher in-hospital mortality and MI-rate. After correction for differences in baseline characteristics as well as in treatment strategy patients with NSTEMI had a more than 4-fold increased risk to die during the index hospital stay (HR 4.19, $p<0.001$).
Conclusions: Patients presenting NSTE-ACS and troponin release are known to be at high risk. These NSTEMI-patients were more often treated by coronary intervention. However, NSTEMI was an independent predictor of hospital mortality in the patient population with NSTE-ACS with a more than 4-fold increased rate of death.

P5505 | BEDSIDE
Relative prognostic significance of self-reported frailty components in non-ST-segment elevation acute coronary syndromes: men and women are not the same

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Purpose: Frailty is associated with worse morbidity and mortality in CVD; however, the prognostic value of self-reported frailty components is unclear. In the TRILOGY ACS trial of medically managed ACS patients, elderly participants (≥65 y) were asked if they had experienced any Fried Frailty Index component in the last 12 mos: unintentional weight loss ≥5 kg (WL); decreased grip strength (GRIP); increased fatigue/lethargy (F-L); slower 5-m walking pace (WALK); or decreased physical activity (PA). We examined 1) contributions of individual frailty components to risk of all-cause mortality and 2) whether this association is modulated by age and sex.
Methods: Cox proportional models were used to examine associations between frailty components and time to death. The impact of age and sex on Fried categorization (not frail; pre-frail [1-2 components]; and frail [≥3 components]) was examined.
Results: Of 4996 elderly patients, 89 (1.8%) had WL, 211 (4.2%) had GRIP, 523 (10.5%) had F-L, 489 (9.7%) had WALK, and 975 (19.5%) had PA. Overall, 3612 (72.3%) were not frail, 1147 (23%) were pre-frail, and 237 (4.7%) were frail. The distribution of frailty and its components was similar between sexes and increased with age. HRs for association of self-reported frailty components with mortality was: WL, 1.96, $p<0.01$; WALK, 1.78; $p<0.01$; PA, 1.64; $p<0.01$; F-L, 1.53; $p<0.01$; GRIP, 1.29; p=0.20. However, the components did not offer additive prognostic power. The association between frailty categorization and mortality was modulated by age and sex (Fig. 1).
Conclusions: A simple frailty self-assessment offers important prognostic information on mortality. Equal weighting of frailty components deserves reexamination. Self-reported frailty may offer more prognostic information in men than in women.

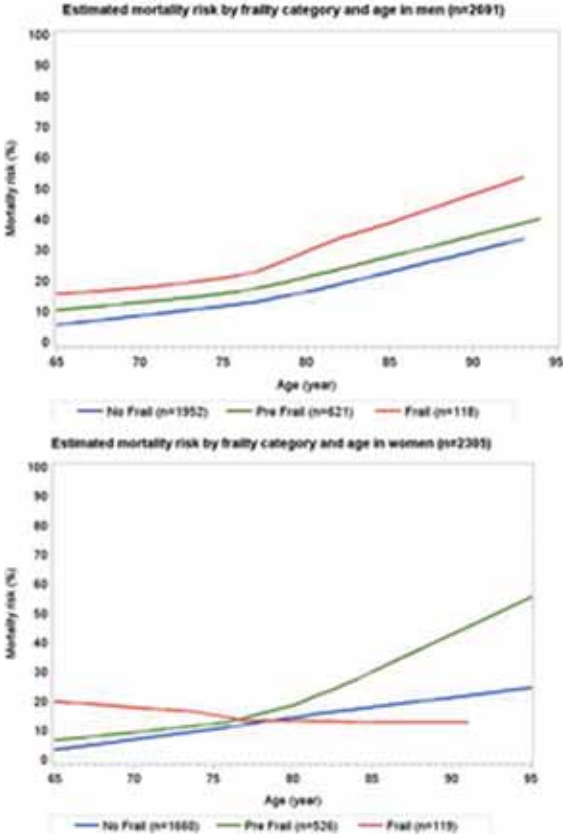

Figure 1. Frailty and mortality risk.

THROMBOSIS AND ANTICOAGULATION – I

P5507 | BEDSIDE
Bayesian meta-analysis of the efficacy and safety of the novel aral anticoagulants for treatment of venous thromboembolism

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Purpose: Traditional extended treatment of venous thromboembolism (VTE) has relied on the use of vitamin K antagonism for prevention of recurrent VTE after initial diagnosis. The use of warfarin in this patient population has challenges including risk of significant bleeding, drug interactions, and frequent monitoring. While new oral anticoagulants have been tested as alternatives to warfarin, the extent of longitudinal benefit and safety remains unclear. We sought to examine this controversy by performing a Bayesian meta-analysis.
Methods: A literature search was performed which identified a total of 16,117 patients from 5 randomized controlled trials comparing the novel oral anticoagulants (apixaban, edoxaban, rivaroxaban and dabigatran) to warfarin. Frequentist and Bayesian random effects models were utilized to evaluate the primary efficacy endpoints of recurrent VTE and mortality, VTE related death and mortality, in addition to safety endpoints of major bleeding and clinically-significant minor bleeding.
Results: For the primary combined endpoint of recurrent VTE and mortality, there was a 62% probability of benefit, with a posterior odds ratio of 0.6593 (Bayesian credible interval 0.27-1.54). The combined safety endpoint of major bleeding and clinically relevant minor bleeding was found to have a 42% probability of benefit, with posterior odds ratio of 1.35 (Bayesian credible interval 0.61- 2.51). Additional clinical and safety endpoints did not demonstrate significant differences, though a trend towards benefit with the novel oral anticoagulants was seen.
Conclusions: Sequential Bayesian meta-analysis of the novel anticoagulants versus warfarin in treatment of venous thromboembolism supports the safety and efficacy of using the novel oral anticoagulants as primary therapy for VTE. There is a non-significant trend towards increased efficacy of the novel oral agents, though this is tempered by a non-significant trend towards increased bleeding events.

P5508 | BENCH
Macrophages and platelets are the major source of the Factor Seven Activating Protease (FSAP) in human atherosclerotic plaques: a possible crosslink between inflammation and coagulation

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Purpose: Factor VII activating protease (FSAP) activates FVII as well as prourokinase, thus regulating local proteolysis-, hemostasis- and remodelling associated processes in the vasculature. In order to define the role of FSAP in vascular pathophysiology we have investigated the expression of FSAP protein in atherosclerotic plaques with defined clinical features.
Methods: 36 carotid atherosclerotic plaques were harvested during carotid endarterectomy, immunohistochemically and semi-quantitavely examined for the presence of macrophages (CD68), platelets (CD41) and FSAP. Patients' demographics were recorded and blood samples were stored. Human macrophages were isolated and stimulated with defined concentrations of oxLDL and several statins. Stimulated and non stimulated human platelets underwent further analysis and FSAP signals were ascertained at both messenger and protein levels.
Results: FSAP protein was found to be associated with CD68 expressing cells in macrophage-rich shoulder regions in early noncomplicated plaques. A stronger FSAP signal was observed in advanced symptomatic lesions, focally accumulated in intraplaque hemorrhage-related structures within the necrotic core of atherosclerotic plaques. ($p<0.05$, compared to non-complicated asymptomatic plaques). Platelets were identified as the main sources of FSAP within atherothrombotic material. Unstimulated platelets, isolated from healthy subjects, showed a small amount of FSAP mRNA and protein and ADP, but not TRAP, induced FSAP expression in activated platelets. Interestingly, agonist-induced FSAP expression was partially inhibited by aspirin. Furthermore, human foam cells expressed FSAP in vitro and this was further induced by different statins.
Conclusions: Platelets and monocytes/macrophages are a major source of FSAP in human atherothrombotic plaques. Human foam cells and activated platelets expressed FSAP in vitro. These findings suggest that FSAP could serve as a molecular link between lipid metabolism, inflammation, and thrombus formation, which are all features of atherosclerotic plaques.

P5509 | BEDSIDE

Treatment of acute pulmonary embolism with dabigatran or warfarin: a pooled analysis of efficacy data from RE-COVER and RE-COVER II

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Purpose: In the RE-COVER and RE-COVER II trials, dabigatran etexilate (DE) was as effective as warfarin (W) for treatment of acute VTE, with a lower risk of bleeding. In this pre-specified subgroup analysis of pooled data from RE-COVER and RE-COVER II, we investigated the efficacy of DE versus W according to the index event type (symptomatic pulmonary embolism [PE] with/without deep vein thrombosis [DVT], or DVT alone).

Methods: Patients with acute, objectively verified, symptomatic proximal DVT without symptoms of PE or with symptomatic PE received parenteral anticoagulation and were randomized to W or placebo for ≥5 days, until the international normalized ratio (INR) was ≥2 at two consecutive measurements. After discontinuing parenteral therapy, patients continued W (target INR 2.0–3.0) or received DE 150 mg twice daily (double-dummy) for 6 months. The primary efficacy outcome was the first recurrent, symptomatic, objectively confirmed VTE/ VTE-related death from randomization to the end of the pre-specified post-treatment follow-up. Outcome events were adjudicated centrally.

Results: Recurrent VTE/VTE-related death occurred in 68/2553 (2.7%) of all patients on DE and 62/2554 (2.4%) on W; hazard ratio 1.09 (95% CI 0.77, 1.54). This included symptomatic fatal or non-fatal PE in 20/2553 (0.8%) patients on DE and 21/2554 (0.8%) on W. The table shows event rates according to index event. Cox regression analyses showed no statistically significant interaction (P=0.4848), indicating similar treatment effects regardless of index event.

Outcomes by treatment and index event

Symptomatic PE as index event	VTE or VTE-related death (including DVT and/or PE) Patients, n/N (%)		PE (fatal or non-fatal)* Patients, n/N (%)	
	Dabigatran	Warfarin	Dabigatran	Warfarin
No	45/1758 (2.6)	37/1747 (2.1)	11/1758 (0.6)	10/1747 (0.6)
Yes	23/795 (2.9)	25/807 (3.1)	16/795 (2.0)	16/807 (2.0)

*Subset of VTE/VTE related deaths.

Conclusion: The incidence of recurrent PE was numerically greater in patients with PE at baseline than in those with proximal DVT independent from the treatment. DE was as effective as W regardless of whether patients initially presented with PE or with DVT. The risk of recurrence was similar in patients who presented initially with PE or DVT, however, a recurrent VTE was more likely to be a PE if the initial event was a PE. DE was as effective as W in prevention of recurrent PE and DVT.

P5510 | BEDSIDE

Expression of genes in aspirated coronary thrombi in patients with acute myocardial infarction

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Purpose: Althought data about the clinical benefit of thrombus aspiration have exhibited controversial results, the knowledge of thrombus composition, particularly with respect to genetics, is of increasing interest. Reports until now have mainly focused on the structural and cellular components of aspirated coronary thrombi. We therefore aimed to investigate the genetic expression of selected mediators and proteases actively involved in plaque rupture, platelet and neutrophil cell activation, coagulation, fibrinolysis and inflammation in aspirated coronary thrombi from patients with acute myocardial infarction.

Methods: Coronary thrombi from 67 patients with acute myocardial infarction were investigated. RNA from aspirated coronary thrombi was isolated and gene expression arrays of selected markers were performed by a RT-PCR based method with relative quantification.

Results: Twenty of 22 selected markers were expressed in >50% of the samples. CRP and IL12 were not expressed. The relative quantification of P-selectin correlated negatively to the ischemic time (p=0.01), while genes related to fibrinolysis (t-PA, u-PA, PAI-1), inflammation (PTX3, CXCL9, MCP-1, IL18, TNF-alfa) and to plaque instability (MMP-2 and TIMP-1) correlated positively to the ischemic time (all <0.05). When dichotomizing ischemic time into ≤ median (4.0h) and > median, the relative reduction of P-selectin was 0.7-fold, while the relative increase in t-PA was 2.2-fold, u-PA 5.8-fold, PAI-1 8.7-fold, PTX3 1.7-fold, CXCL9 3-fold, MCP-1 2.6-fold, IL18 2.3-fold, TNF-alfa 2-fold, MMP-9 2.8-fold and TIMP-1 3.2-fold. The presence of type 2 diabetes increased PAI-1 expression 3.2-fold, while the presence of hypertension reduced IL-8 and TIMP-1 to about half-fold. Smoking and overweight did not affect any markers.

Conclusions: Several pro-inflammatory markers and mediators were genetically expressed in aspirated coronary thrombi from patients with acute myocardial infarction. The genetic expression profile changed according to the ischemic time with a decrease in expression of genes related to platelets and an increase in expression of genes related to fibrinolysis, inflammation and plaque instability, respectively. Expression of PAI-1 was significantly higher in patients with type 2 diabetes, possibly confirming the particular role of impaired fibrinolysis in type 2 diabetes. The presence of hypertension seemed to be associated with plaque instability.

P5511 | BEDSIDE

Markers of thrombin generation are associated with myocardial necrosis and left ventricular impairment in patients with ST-elevation myocardial infarction

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Introduction and aim: Thrombin generation and fibrin formation play an important role in intracoronary thrombus formation, which may lead to an acute myocardial infarction.

Aim of the present study was to investigate whether D-dimer, pro-thrombin fragment 1+2 (F1+2) and endogenous thrombin potential (ETP) as markers of in vivo and ex vivo thrombin generation, respectively, are associated with myocardial necrosis assessed by Troponin T (TnT), and left ventricular impairment assessed by left ventricular ejection fraction (LVEF) and NT-proBNP.

Methods: Patients with ST-elevation myocardial infarction (STEMI) from a cross sectional cohort study (n=993), referred for primary percutaneous coronary intervention (PCI) were included. Median age was 61 years (range 24-94), 80% male. Blood samples were drawn the first morning after admission at a median time of 24 hours after onset of symptoms. D-dimer and F1+2 were determined by ELISA and ETP by the CAT-assay. Patients on warfarin were excluded from analysis.

Results: In the total population levels of D-dimer, F1+2 and ETP (median (25,75 percentiles)) were 456 ng/L (287,796), 246 pmol/L (178,356), 1564 nM (1366,1743), respectively.

Significant correlations were found between both peak TnT and D-dimer (r=0.260, p<0.0001) and F1+2 (r=0.364, p<0.001) and between NT-proBNP and D-dimer (r=0.243, p=0.001) and F1+2 (r=0.120, p=0.0001). When dividing TnT and NT-proBNP levels into quartiles there were significant trends for increased levels of both markers across quartiles (all p<0.0001). No significant associations between TnT, NT-proBNP and ETP were found. When adjusting for relevant covariates (age, gender, BMI and NT-proBNP), both D-dimer and F1+2 remained significantly associated with peak TnT (both p=0.0001).

D-dimer remained significantly associated with NT-proBNP after adjustments (p=0.001), whereas the association between NT-proBNP and F1+2 was no longer statistically significant (p=0.301). A weak, but statistically significant inverse correlation was found between LVEF and D-dimer (r=0.160, p=0.0001) and F1+2 (r=0.090, p=0.011). When dichotomizing LVEF levels at 40%, we observed significantly higher levels of both D-dimer (p=0.0001) and F1+2 (p=0.014) in the group with low EF (n=147). No difference in ETP levels was found.

Conclusion: In a large cohort of STEMI patients, levels of D-dimer and F1+2 were significantly associated with the extent of myocardial necrosis assessed by peak TnT. The high levels of these coagulation markers in patients with low LVEF and high NT-proBNP may indicate a hypercoagulable state in patients with impaired myocardial function.

P5512 | BEDSIDE

The management of patients with atrial fibrillation undergoing percutaneous intervention with stent implantation (AFCAS): triple therapy with lmwh bridging is associated with higher risk

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Purpose: Bridging treatment with low-molecular-weight heparin (LMWH) has been the standard recommendation for patients at high risk for thromboembolic events if VKA were interrupted, but this strategy seems questionable in the light of recent findings indicating that bridging increases the risk of haemorrhage without lowering the frequency of periprocedural thromboembolism. Therefore, we prospectively assessed the effect of LMWH-bridging on thrombotic and bleeding events in patients with AF undergoing stent implantation with an indication for triple therapy.

Methods: AFCAS is an observational, multicenter, prospective registry including patients with AF who are referred for percutaneous coronary interventions with stent implantation (PCI-S)). The primary endpoints were a composite of cardiac

and cerebrovascular events (MACCE) and bleeding complications as defined by the BARC-definition from discharge to 1-year follow-up period.
Results: Out of the 975 consecutive patients enrolled, 663 were discharged on triple therapy, either VKA-triple therapy (VKA-TT, n=498) or LMWH-triple therapy (LMWH-TT, n=165). Male gender (70.7% VKA-TT vs. 72.7% LMWH-TT), age (73.0±7.9 VKA-TT vs. 72.5±7.9 years of age LMWH-TT), BMI (28.4±4.5 VKA-TT vs. 28.7±4.9 kg/m^2 LMWH-TT) and other risk factors with the exception of diabetes (32.3% VKA-TT vs. 50.9% LMWH-TT, $p<0.001$) and hypertension (79.7% VKA-TT vs. 95.8% LMWH-TT, $p<0.001$) were not different in comparison of both groups.
The rate of MACCE was significantly elevated in patients discharged on LMWH-TT in comparison to patients discharged on VKA-TT (29.1% vs. 17.3%, p=0.002). In a multivariate cox regression model adjusted for classical risk factors, renal impairment, the presence of anaemia, and acute coronary syndrome patients discharged on LMWH-TT had increased risk for MACCE compared to patients discharged on VKA-TT (HR 1.61, 95%CI 1.05-2.45, p=0.028). Moreover, severe bleedings (BARC >2) were more often but not significantly associated with LMWH-TT during the one year follow-up period (13.3% LWMH-TT vs. 9.2% VKA-TT, p=0.140).
Conclusions: In our large, prospective, real-world population of patients with AF undergoing PCI-S patients discharged on LMWH-TT had a significantly higher risk for the 1-year incidence of MACCE in comparison to patients discharged on VKA-TT.
Our study further supports the idea that bridging therapy with LMWH may be harmful for patients with an indication for PCI-S under oral anticoagulation.

P5513 | BEDSIDE
Impact of dabigatran and phenprocoumon on clopidogrel mediated ADP induced platelet aggregation in patients with atrial fibrillation (The Dabi-ADP-2 trial)

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Background: A relevant number of patients receive triple therapy with clopidogrel, aspirin and oral anticoagulation with either vitamin K antagonists or new oral anticoagulants. Clopidogrel's efficacy on ADP induced platelet function may be influenced by concomitant antithrombotic therapies. The impact of the direct thrombin inhibitor dabigatran etexilate as compared to phenprocoumon on platelet function in patients with concomitant clopidogrel therapy is unknown.
Methods: The "Impact of DABIgatran and phenprocoumon on the clopidogrel mediated ADP induced platelet aggregation in patients with atrial fibrillation" (DABI ADP 2) study was a randomized trial performed at Deutsches Herzzentrum Munich, Germany, which enrolled patients with atrial fibrillation who also required dual antiplatelet therapy (DAT). Patients were randomly assigned to receive either dabigatran (n=22) or the vitamin K antagonist phenprocoumon (n=24) in addition to DAT for a 2 week period. The primary endpoint was ADP-induced platelet aggregation (in AU x min) assessed with multiple electrode platelet aggregometry at 14 days after randomization.
Results: There was no significant difference regarding the primary endpoint between both groups, dabigatran 326 [268 - 462] AU x min and phenprocoumon 350 [214-535] AU x min, p=0.70. Furthermore, no significant differences were observed regarding the secondary endpoints, ADPhs- (P=0.70), TRAP- (P=0.17) and COL- (P=0.20) induced platelet aggregation at 14 days.
Conclusion: For all agonists studied here, dabigatran as compared to phenprocoumon has no impact on the ex vivo- measured platelet aggregation in patients with concomitant aspirin and clopidogrel therapy
ClinicalTrials.gov identifier: NCT01352702

P5514 | BEDSIDE
Bivalirudin therapy for acute coronary syndromes and percutaneous coronary intervention: a meta-analysis of randomized trials

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Background: A variety of antithrombotic medications are used in the management of patients with acute phase of coronary syndrome (ACS) undergoing early use of percutaneous interventions (PCI) which attempt to reduce death, myocardial infarction and periprocedural ischemic events, recurrent revascularization and stent thrombosis. The aim of the study was to perform a meta-analysis of randomized trials (RCT) to assess the efficacy and safety of bivalirudin with or without Gp IIb-IIIa compared with unfractionated heparin or enoxaparin plus glycoprotein (GP) IIb/IIIa inhibitors in patients with ACS.
Methods: We obtained results from all RCTs evaluating the benefits of adjunctive bivalirudin as compared to UFH among patients with ACS undergoing an invasive strategy therapy. RCTs were searched in MEDLINE, EMBASE, the Cochrane Controlled Clinical Trial Register and other trial registries, and references of relevant articles. The co-primary endpoints of the analysis were long-term mortality rates. The incidence of major adverse cardiovascular events (MACE), including the composite of death, myocardial infarction (MI), or urgent revascularization, death or MI, as well as stent thrombosis. The safety end-point was major and minor bleeding [according to the Thrombolysis In Myocardial Infarction (TIMI) criteria].
Results: Six RCTs were identified involging 22,291 patients (8991 heparin and 13300 bivalirudin). Anticoagulation with bivalirudin as compared with heparin results in no difference in major adverse cardiovascular events (odds ratio [OR] 1.1, 95% confidence interval [CI] 0.92 to 1.18), death (OR 0.92, 95% CI 0.81 to 1. 27). There is a higher risk of myocardial infarction (OR 1.19, 95% CI 1.02 to 1.30), urgent revascularization (OR 1.31, 95% CI 1.15 to 1.49) and stent thrombosis (OR 1.63, 95% CI 1.34 to 2.01). Regarding, the safety end-point bivalirudin decreased risk of TIMI major bleeding (OR 0.58, 95% CI 0.49 to 0.72) and TIMI minor bleeding (OR 0.52, 95% CI 0.41 to 0.69)
Conclusion: Bivalirudin administration reduces major and minor bleedings when compared with unfractionated heparin or enoxaparin plus GP IIb/IIIa inhibitors. An early ischaemic hazard disfavouring bivalirudin was noted when compared with unfractionated heparin or enoxaparin.

P5515 | BEDSIDE
Impact of recommendations of guidelines in patients with atrial fibrillation submitted coronary stenting

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Objective: To assess the impact of dual antiplatelet therapy (DAPT: clopidogrel and ASA) with warfarin (triple therapy: TT) vs DAPT in patients with non-valvular atrial fibrillation (AF) submitted to PCI with stenting (PCI-S) regarding to CHADS2, CHA2DS2VASc and HASBLED scores.
Methods: A prospective multicenter study was conducted from 2007 to 2011 to identify patients with non-valvular AF who underwent PCI-S. Baseline clinical characteristics, CHADS2, CHA2DS2VASc, HASBLED scores, PCI details, antithrombotic therapy at discharge and its duration were recorded. Follow-up was 1 year. All bleeding events, thromboembolisms (stroke or systemic embolism, acute myocardial infarction, target revascularization), and death were analyzed post hoc.
Results: We identified 585 patients with AF (74.8% male, 73.11±8 years); 319 (54.5%) received TT and 266 (45.5%) DAPT. Duration of TT and DAPT was similar: 4.4±4 and 4.0±2.2 months, respectively. Baseline characteristics were similar in both groups, except for a higher rate of HTA (79% vs 69.5%, p=0.006), previous PCI (40.3% vs 23.6%, p=0.0001) and previous stroke (17.9% vs 10.5%, p=0.008) in the TT group. Patients with TT showed a higher rate of CHADS2 score ≥2 (70.8% vs 59.4%, p=0.002) but similar rates of CHA2DS2VASc ≥2 (74.6% vs 71.4%, p=0.25) and HASBLED≥3 (27.2% vs 24.1%, p=0.22). Thromboembolism rate was higher in patients on DAPT (1.6% vs 5.6%, p=0.006). The 80% of patients with a thromboembolism and treated with DAPT had a CHADS2 score ≥2 (median 2, range 1-4) and 93.3% a CHA2DS2VASc score ≥2 (median 4.5, range 3-5). Total bleedings were more frequent in patients with TT (21% vs 13.5%, p=0.01) with an excess of major bleeding (7.2% vs 2.3%, p=0.004). Among patients treated with TT and presenting with a bleeding event, 16 (23.8%) had a CHA2DS2VASc =1. In addition, in overall patients who had a bleeding event, 31.8% had a HASBLED ≥3. Fifty-two patients (8.9%) died during follow-up, 14 (26.9%) while receiving TT, and 3 of them had a CHA2DS2VASc =1. Multivariate analysis identified as independent predictors for mortality: age (HR 1.04; 95% CI 1.00-1.09, p=0.04), renal failure (HR 3.16; 95% CI 0.87-3.30, p=0.0001), heart failure (HR 1.99; 95% CI 1.11-3.56, p=0.01), and TT (HR 2.91; 1.33-6.35, p=0.007). CHA2DS2VASc score was not predictor (HR 0.84: 95% CI 0.35-1.98, p=0.69).
Conclusions: In patients with non-valvular AF who undergo PCI-S, the decision of treatment with TT or DAPT is not always influenced by CHADS2, CHA2DS2VASc or HASBLED scores. In patients with low-moderate thromboembolic risk, DAPT should be considered as an alternative to TT.

P5516 | BEDSIDE
The association of deep venous thrombosis with atherosclerosis depends on a concomitant history of pulmonary embolism

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Purpose: Venous thromboembolism comprises deep venous thrombosis (DVT) and pulmonary embolism (PE). Clinical studies have shown an association between atherosclerosis and DVT. It is still not clear, however, if DVT patients with concomitant history of PE have the same clinical risk profile than DVT patients without PE. Therefore we investigated the clinical profile of DVT patients stratified for the presence of a concomitant history of PE.
Methods: Data from the observational, multi-center thrombEVAL trial (NCT01809015) of patients with oral anticoagulation treatment were analysed for this work.
Results: The overall sample (n=2,318) comprised 305 patients with isolated DVT and 204 DVT patients with concomitant history of PE. The age (isolated DVT: 70.0

(IQR 57.0/78.3) vs. 70.0 (54.0/77.0) years in DVT+PE group, P=0.49) and gender distribution (47.5% males with isolated DVT vs. 49.0% males with DVT+PE, P=0.79) were comparable between both groups. Individuals with isolated DVT had a higher prevalence of diabetes (28.2% vs. 16.3%, P=0.0019), myocardial infarction (19.4% vs. 11.8%, P=0.027), coronary artery disease (CAD; 32.3% vs. 17.8%, P=0.00036), heart failure (HF; 28.9% vs. 18.2%, P=0.0062), atrial fibrillation (AF; 40.1% vs. 23.0%, P<0.0001) and peripheral artery disease (PAD; 21.3% vs. 10.9%, P=0.0024). Consequently, they had more symptomatic atherosclerosis (CAD, MI or PAD) (42.9% vs. 26.4%, P=0.00019) and a higher Charlson comorbidity index (5.59±3.10 vs. 4.93±3.05, P=0.017), but a lower BMI (27.5 (24.3/30.9) vs. 28.7 (25.6/31.9) kg/m^2, P=0.0078) than those with concomitant PE.

In multivariable regression models, diabetes (OR, 2.28; 95% CI [1.39-3.72], P=0.0010), CAD (OR, 1.75 [1.02-2.99], P=0.042), AF (OR, 2.35 [1.40-3.94], P=0.0012) and systemic atherosclerosis (OR, 1.89 [1.17-3.06], P=0.0097) were independently associated with isolated DVT. Obesity (OR, 0.60 [0.40-0.91], P=0.15) and chronic kidney disease (OR, 0.53 [0.30-0.92], P=0.024) were associated with DVT with a concomitant history of PE.

Conclusions: A concomitant history of PE is an important discriminator for the clinical profile of individuals with history of DVT. Isolated DVT is associated with symptomatic atherosclerosis, especially with diabetes, CAD and AF.

THROMBOSIS AND ANTICOAGULATION – II

P5518 | BEDSIDE
Rivaroxaban in patients after an acute coronary syndrome with cardiac biomarker elevation: insights from the ATLAS ACS 2-TIMI 51 trial

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Purpose: The ATLAS ACS 2-TIMI 51 trial randomized 15,526 patients to treatment with the factor Xa inhibitor rivaroxaban or placebo after an index acute coronary syndrome (ACS) event. We have previously reported the results in the total population. Here, we present the results in patients with cardiac biomarker elevation during their index ACS event, who comprise a large and medically important subgroup in the trial.

Methods: In the double-blind, placebo-controlled ATLAS ACS 2-TIMI 51 trial, patients were randomized to twice daily dosing of either rivaroxaban 2.5 mg, rivaroxaban 5 mg, or placebo for a median of 13 months and up to 31 months. Cox proportional hazard models were used to generate hazard ratios (HR) and 95% confidence intervals (CI), and rates are presented as 2-year Kaplan-Meier estimates.

Results: In total, 12,626 patients in the trial experienced cardiac biomarker elevation during their index ACS event. Among this group, rivaroxaban (combined doses) reduced the primary efficacy endpoint of cardiovascular death, MI, or stroke by 19% as compared with placebo (9.1% vs. 11.5%, HR 0.81, 95% CI 0.71-0.93, P=0.003). Among the remaining patients without cardiac biomarker elevation, rivaroxaban (combined doses) vs. placebo resulted in a HR of 1.06 (95% CI 0.74-1.51, P=0.74). Evaluating patients with cardiac biomarker elevation, both rivaroxaban 2.5 mg twice daily and 5 mg twice daily as compared with placebo reduced the primary efficacy endpoint (9.7% vs. 11.5%, P=0.021 and 8.6% vs. 11.5%, P=0.008, respectively). Furthermore, rivaroxaban 2.5 mg twice daily as compared with placebo resulted in a significant reduction in cardiovascular mortality (2.5% vs. 4.5%, P<0.001) and all-cause mortality (2.8% vs. 4.8%, P<0.001) within this group. Among patients with cardiac biomarker elevation, rivaroxaban (combined doses) as compared with placebo increased the rates of TIMI major bleeding not related to CABG (2.2% vs. 0.7%, P<0.001) without a significant increase in fatal bleeding (0.3% vs. 0.3%, P=0.83); rivaroxaban 2.5 mg twice daily resulted in less fatal bleeding than rivaroxaban 5 mg twice daily (0.1% vs. 0.5%, P=0.007).

Conclusion: Among patients with a recent ACS and cardiac biomarker elevation, rivaroxaban reduced cardiovascular events. The 2.5 mg twice daily dose resulted in a significant survival benefit as compared with placebo and less bleeding as compared with the 5 mg twice daily dose. Thus, the addition of 2.5 mg twice daily of rivaroxaban could represent a new treatment strategy in patients with a recent ACS and cardiac biomarker elevation, in accordance with the EMA recommendation.

P5519 | BENCH
Cancer associated microthrombosis; a contributing factor to troponin elevation in acute ischemic stroke

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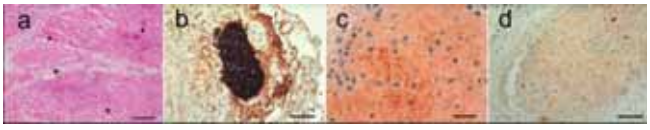
Purpose: Troponin elevation in acute ischemic stroke (AIS) is common and has repeatedly been associated with an increased risk of mortality. The underlying pathophysiology is however not fully clarified, although a number of possible explanations have been suggested, such as coexisting acute coronary artery disease or a neurogenic cardiac damage due to sympathoadrenal activation. In our ongoing study (The Impact of Stroke on Heart Function) we seek to identify possible mechanisms behind troponin elevation in AIS.

Methods: The study is based on diagnostic methods ranging from clinical assessment and radiology to laboratory methods including flow cytometry and histopathological investigation to seek underlying mechanisms behind unexplainable high levels of plasma troponin.

Results: We have identified a previously not recognized mechanism; a malignancy associated hypercoagulative state, presenting with ischemic stroke and high levels of plasma troponin T. Autopsy with histopathology in two cases revealed adenocarcinomas with cerebral and myocardial microthrombosis (fig a). Analysis showed markers of cancer associated thrombosis with tissue factor in both metastases (fig b) and thrombi. We could also show, to the best of our knowledge for the first time in human, microvesicles staining positive for the tumour marker CK18, and citrullinated histone H3, markers of the recently described cancer associated procoagulant DNA-based neutrophil extracellular traps (NETs) in thrombi in the heart (fig c), lung and brain (fig d).



Conclusion: Our results identify cancer associated microthrombosis as a previously unrecognized contributing factor to high levels of troponin in AIS. We believe that unexplainable high levels of troponin in acute stroke deserve special attention in terms of possible occult malignancy.

P5520 | BEDSIDE
Rivaroxaban in elective percutaneous coronary intervention to treat stable coronary artery disease

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Rivaroxaban in elective percutaneous coronary intervention to treat stable coronary artery disease.

Background: Patients on rivaroxaban in the need of a percutaneous coronary intervention (PCI) represent a clinical conundrum.

Aims: To investigate if rivaroxaban, with or without an additional bolus of unfractionated heparin (UFH), could suppress coagulation activation during PCI.

Methods and results: This phase-IIa, multi-center, randomized, open-label study included 107 patients undergoing an elective PCI (EudraCT. Unique identifier: No: 2011-001094-58). Patients on stable dual antiplatelet therapy were randomized (2:2:2:1) to either pre-procedural rivaroxaban 10mg (n=30) or 20mg (n=32), or rivaroxaban 10mg plus UFH (n=29) as compared to standard periprocedural UFH (n=16). Blood samples for markers of thrombin generation were drawn prior to and at 0, 0.5, 2, 6-8, 48 hours after start PCI.

In the rivaroxaban, and the rivaroxaban plus heparin treated patients, the levels (median, interquartile range) of prothrombin fragment 1 + 2 at 2 hours post-PCI were 0.16 nmol/L (IQR: 0.1) and 0.17 nmol/L (IQR: 0.2) respectively. Thrombin-antithrombin III (TAT) complex at 2 hours post-PCI were 3.90 μg/L (IQR: 6.8) and 3.90 μg/L (IQR: 10.1) respectively remaining below the upper limit of normal (ULN) following PCI and stenting. This was similar to the control group of UFH treatment alone. However, median values for TAT-complex passed above the ULN with increasing tendency starting at 2 hours post-PCI in the UFH alone arm, but not in the rivaroxaban treated patients, with the highest result at 48 hours post-PCI (9.00 μg/L, IQR: 20.5).

Numerically, there were fewer thrombotic events and less bleeding complications with rivaroxaban. Major bleeding events did not occur in any treatment group.

Conclusion: Rivaroxaban effectively suppresses coagulation activation after elective PCI and stenting and without signal towards an excess of actionable bleeding events as compared to UFH.

P5521 | BEDSIDE
Incidence and predictors of cardiovascular events in patients with systemic lupus erythematosus (SLE): a systematic review and meta-analysis

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Background: Cardiovascular disease represents an important cause of morbidity and mortality in patients with a diagnosis of systemic lupus erythematosus (SLE), due to a complex interplay between traditional risk factors and disregulation of

autoimmunity, but uncertainty is still present about the most important predictors of cardiovascular events.
Objectives: Aim of our work is therefore to perform a collaborative systematic review on incidence and predictors of cardiovascular events in SLE patients.
Methods: PubMed, Cochrane was systematically searched for eligible studies on SLE and cardiovascular events between January 2008 and December 2012. Study features, patient characteristics, and incidence of stent thrombosis were abstracted and pooled, when appropriate, with random-effect methods (point estimate [95% confidence intervals]),and consistency of predictors was formally appraised.
Results: A total of 17187 patients were included; of those, 93.1% were female, and the median age was of 39 years. After a median follow-up period of 8 years, cardiovascular events presented in 25.4%, including acute myocardial infarction (4.1%) and stroke (7.3%). The most important predictors may be divided in traditional risk factors, like male gender (OR 6.2, CI 95% 1.49 - 25), hyperlipaemia (OR 3.9, CI 95% 1.57 – 9.71), familiar history of cardiac disease (OR 3.6, CI 95% 1.15 – 11.32) and hypertension (OR 3.5, CI 95% 1.65 – 7.54),and SLE-related features, like the presence of auto-antibodies (OR 5.8 and 5.0, CI 95% 3.28 – 7.78) and neurological disorders (OR 5.2, CI 95% 2.0 – 13.9). A low correlation was shown for importance of organ damage and SLE activity (respectively OR 1.4, CI 95% 1.09 – 4.44 and OR 1.2, CI 95% 1.2 – 1.2), as well as for the age at diagnosis (OR 1.1, CI 95% 1.07 – 1.17).
Conclusions: Cardiovascular events in SLE patients are caused by a multifactorial mechanism, including both traditional and disease-specific risk factors. A global valuation with an individual risk-stratification based on both these features is important to correctly manage these patients in order to reduce negative outcomes.

P5522 | BEDSIDE
Role of bivalirudin in radial coronary interventions: a meta-analysis of observational studies

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Purpose: Benefit of bivalirudin for patients undergoing percutaneous coronary intervention has been demonstrated over heparin, although still not conclusive evidence has been provided about interaction between anticoagulation and site of access.
Methods: All studies investigating patients undergoing radial or femoral PCI and comparing bivalirudin and heparin (with or without GPI) were included in the present review. Major bleeding was the primary end point, with death, MACE (a composite end point of death, myocardial infarction and target vessel revascularization) and NACE (Net Adverse Clinical Events) the secondary ones.
Results: 6 studies with 521638 patients were included. Median age was 63 years old (61-65); 26% (24-28) of the patients were female, 21% (17-32) had diabetes mellitus and 17% (12- 21) renal disease. During hospitalization, bivalirudin reduced risk of bleeding, both for patients with femoral (OR 0.73 [0.60, 0.90]) and radial (OR 0.51 [0.43, 0.60]) access. Death and MACE rates, on the contrary, were not reduced by bivalirudin, both for radial (OR 0.86 [0.69, 1.07] and 0.86 [0.53, 1.39] respectively) and for femoral (OR 1.07 [0.74, 1.56] and 0.24 [0.04, 1.59] respectively). Similarly, rates of NACE did not differ in the two groups (0.87 [0.38, 1.96] and 0.70 [0.49, 0.98], all CI 95%).
Conclusions: Benefit of bivalirudin for reduction of bleeding is consistent both for radial and for femoral access.

P5523 | BENCH
Prothrombotic properties of Dabigatran-treated blood under flow

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Purpose: In patients with atrial fibrillation, oral anticoagulation with dabigatran in contrast to VKAs (vitamin K antagonists) associates with a numerical increase in acute coronary syndromes. Whether this observation is due to a play of chance or linked to so far undefined prothrombotic actions of dabigatran remains unclear. We therefore asked whether platelet functionality under flow conditions is altered in dabigatran-treated blood.
Methods and results: We analyzed platelet function in patients receiving either dabigatran 150mg bid or dose adapted VKA. Despite higher thrombin levels in the dabigatran group we found a normal whole blood aggregation and platelet reactivity under static conditions as determined by impedance based aggregation (n=15) and flow cytometry assays for P-selectin and active αIIbβIIIA surface expression (n=14). However, aggregate formation on collagen-coated flow-chambers was accelerated and increased after 3 min of perfusion of dabigatran (n=15) compared to VKA (n=14) treated blood. We show that this effect depends on the augmented formation of platelet GPIb-thrombin interactions, which was shown by using GPIb blocking antibody or control antibody respectively. To ask whether these findings are of in vivo relevance we performed a mouse model of arterial thrombosis, using carotid artery ligation. We found an increased platelet aggregation under dabigatran (n=9) compared to vehicle treatment (n=9). Furthermore thrombus stability upon wire injury was increased under dabigatran as reoccurrence of flow appeared in only one animal receiving dabigatran (n=9) compared to all control animals (n=6).
Conclusions: Dabigatran accelerates platelet aggregate formation on extracellular matrix proteins under flow conditions in vitro and in mice in vivo. This involves binding of thrombin to the platelet GPIb receptors. The pathway identified here might contribute to the increase in acute coronary syndromes observed clinically in patients treated with dabigatran.

P5524 | BENCH
No signal for higher risk of myocardial infarction with apixaban: meta-analysis of randomized controlled trials

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Purpose: The coagulation system contributes greatly to the evolution of myocardial infarction (MI). Anticoagulation may reduce the occurrence of MI as monotherapy or with concomitant use of aspirin. Activated factor X antagonists (anti-Xa) and direct thrombin inhibitors have promising results in various indications in multiple non-inferiority trials. However, heterogeneous results were found regarding their cardiovascular safety. We systematically evaluated the risk of MI and mortality in patients receiving the new-generation oral anti-Xa agent apixaban.
Methods: Electronic databases were searched to find prospective, randomized, controlled clinical trials (RCT) that evaluated the clinical impact of apixaban. Efficacy measures included frequency of MI, cardiovascular and overall mortality. Outcome parameters of RCTs were pooled with a random-effects model.
Results: Between January 2000 and December 2013, twelve RCTs comprising 54,054 patients were identified. Based on the pooled results, there was no increase in the risk of MI in patients treated with apixaban (Odds Ratio (OR): 0.90; 95% Confidence Interval (CI) 0.78-1.04; p=0.17) compared to different controls. Cardiovascular and overall mortality with apixaban was comparable to the control groups (OR: 0.88; 95% CI 0.72-1.06; p=0.18, OR: 0.89; 95% CI 0.77-1.03; p=0.11, respectively). The pooled risk of major bleeding was lower in the apixaban treated groups (OR: 0.85; 95% CI 0.64-1.12; p=0.24), however, this reached significance only in subgroup analysis of trials with anticoagulant regimes in the control (OR: 0.68; 95% CI 0.53-0.88; p=0.003).
Conclusions: In a broad spectrum of patients and compared to different controls apixaban treatment was not associated with an increase in myocardial infarction or mortality.

P5525 | BEDSIDE
Comparison of fondaparinux and enoxaparin for non ST elevation acute coronary syndromes - an evaluation in a real world population

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Introduction: In the clinical trials setting, fondaparinux was more effective than enoxaparin in patients with non ST elevation acute coronary syndromes (NSTEACS). However, few observational studies were done to assess the effect of fondaparinux in routine clinical practice.
The aim of this study was to evaluate the effect of fondaparinux, in comparison with enoxaparin, in the in-hospital outcome of an unselected population of NSTEACS patients.
Methods: We performed an observational study of all NSTEACS patients treated with fondaparinux or enoxaparin included in a nation-wide registry, since October 2010. Eighteen patients treated with both fondaparinux or enoxaparin were excluded and data from 3298 patients treated with enoxaparin and 875 with fondaparinux was analyzed. The incidence of in-hospital death, re-infarction, stroke and major bleeding was compared in the two groups of patients. A combined efficacy endpoint of death, re-infarction and stroke was considered. Adjusted odds ratio (OR) for the combined endpoint were computed using logistic regression models.
Results: Fondaparinux treated patients were younger than patients in the enoxaparin group (66$\pm$12 vs. 68$\pm$13 years, $p<0.001$). Coronary angiography was performed in 79.6% of patients in the fondaparinux group and 85.3% in enoxaparin group ($p<0.001$); percutaneous coronary intervention (PCI) was done in 47.3% of fondaparinux group patients and 50.9% of the enoxaparin group (p=0.056). Comparing with enoxaparin group, fondaparinux group had a lower rate of in-hospital stroke (0.2% vs. 0.9%, p=0.046) and death (1.1% vs. 2.7%, p=0.008). No significant differences were found in the incidence of re-infarction (1.4% vs. 2.0%, p=0.24) or major bleeding (1.0 vs. 1.4%, p=0.43). In multivariate analysis, adjusting for age, admission systolic blood pressure, ST-segment changes, use of non fractionated heparin, left ventricle ejection fraction, coronary angiography and PCI, risk of the combined endpoint was significantly lower in fondaparinux treated patients (OR: 0.43, 95%CI: 0.25-0.74, p=0.003).
Conclusions: In this "real world" population of NSTEACS patients, fondaparinux

was associated to a significantly lower risk of death and ischemic complications, without an increase in major bleeding events.

P5526 | BEDSIDE
Novel oral anticoagulants (NOAC) show the anticoaglant action without excess suppression of thrombin

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Background: NOAC acts the effects of anticoagulant without the adverse effects.
Objectives: The aim was to compare NOAC (rivaroxaban;R, dabigatran; D) with warfarin (W) using anticoagulant benchmarks (thrombomodulin; TM, D-dimer; D-D, thrombin-antithrombin complex; TAT, prothrombin-fragment 1+2; PT F1+2).
Subjects: The blood concentration of benchmarks were measured in 28 cases taking R, in 76 cases taking W, in 60 cases taking dabigatran and in 477 cases as the control.
Method: During the administration of R, the TM (TM-R) was measured in 28 cases (total 69 samples). The TM (TM-N) was able to be measured without any anticoagulants in 8 out of the 28 cases (25 samples), and in 13 out of the 28 cases (84 samples) while taking W (TM-W). In 60 cases taking D, who belonged another group, the TM (TM-D) was measured.
Result: TM-N (mean ± SD, 3.20±0.82 FU/ml) was higher in patients with atrial fibrillation (AF) than the control (TM-C: 2.97±0.74). That means that AF might impair the atrial endothelium due to remodeling. Furthermore, TM-R (3.22±0.92 FU/ml) was higher than TM-W (2.93±0.82), TM-all W (2.69±0.69) and TM-D (2.95±0.85). Significantly good relationships were observed between TM-N and TM-R (R=0.701), and between TM-W and TM-R (R=0.779), but TM-R was higher than both TM-N and TM-C (1.3 and 0.73 FU/ml higher). In addition, the D-D was high duaring the pre-medication period, but decreased with W and R and became within nearly normal range. After administration of D, D-D was also within normal range. The TAT decreased with W, R and D. These findings suggest that the higher TM-R may be related to active TM and not the degradation of TM. PT-F 1+2 was clearly high during the pre-medication (339±163 pmol/l), but decreased with W (84±44) and R (168±80). D also suppressed PT-F1+2 (171±111) to almost the same level by R. However, W suppressed it strongly compared to R and D. These findings revealed that W, R and D suppressed the coagulation equally, but if PT-F1+2 reflects the amount of thrombin, R and D may not suppress it completely. These findings suggest that R and D show the anticoagulant action as W equally without reverse effects of the bleeding due to excess suppression of thrombin by W. Furthermore, that suggests R may have an anticoagulant action in addition to thrombin suppression which may be due to the TM-thrombin complex because of the elevation of TM.
Conclusion: NOAC has certainly the anticoagulant action without adverse effects of bleeding because avoiding excess suppression of thrombin.

P5527 | BEDSIDE
Apixaban for the treatment of venous thromboembolism in cancer patients: data from the AMPLIFY trial

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Purpose: Using data from AMPLIFY, a phase III trial comparing apixaban with conventional anticoagulant treatment in patients with venous thromboembolism (VTE), we performed subgroup analyses to compare the efficacy and safety of these regimens in patients with and without active cancer at baseline. Active cancer was defined as cancer that was diagnosed or treated within the past 6 months.
Methods: Patients with symptomatic VTE were randomized to a 6-month course of apixaban (10 mg BID for 7 days followed by 5 mg BID) or conventional treatment consisting of enoxaparin (1 mg/kg BID for at least 5 days) followed by dose-adjusted warfarin (target INR, 2-3). Cancer patients for whom long-term low-molecular-weight heparin (LMWH) was planned were excluded. The primary efficacy outcome was symptomatic VTE or VTE-related death. The intent-to-treat efficacy analysis included all randomized subjects with a non-missing primary endpoint. The primary safety outcome was ISTH-defined major bleeding up to 2 days after stopping study drug in all randomized subjects who received at least one dose of study medication. All outcomes were adjudicated by an independent committee blinded to treatment assignment.
Results: Of the 5395 patients randomized, 169 (3.1%) had active cancer. Baseline characteristics in these patients were similar between the two treatment groups. The median duration of treatment was 167 and 168 days in the apixaban and warfarin groups, respectively. In patients with active cancer at entry, recurrent VTE occurred in 3 of 81 (3.7%) patients in the apixaban group and in 5 of 78 (6.4%) in the warfarin group (relative risk [RR], 0.56; 95% confidence interval [CI], 0.13 to 2.37); major bleeding occurred in 2 of 87 (2.3%) and 4 of 80 (5.0%) patients, respectively (RR, 0.45; 95% CI, 0.08 to 2.46). In patients without cancer at entry, recurrent VTE occurred in 56 of 2528 (2.2%) and in 66 of 2557 (2.6%) patients in the apixaban and warfarin group, respectively (RR, 0.86; 95% CI, 0.60 to 1.22), whereas major bleeding occurred in 13 of 2589 (0.5%) and in 45 of 2609 (1.7%) patients in the apixaban and warfarin group, respectively (RR, 0.29; 95% CI, 0.16 to 0.54).
Conclusions: Although the number of cancer patients was small, the results in this pre-specified subgroup are consistent with the overall findings and suggest that apixaban is as effective as conventional therapy in VTE patients with active cancer, and is associated with less bleeding. Additional studies are needed to compare the efficacy and safety of apixaban and LMWH for VTE treatment in cancer patients.

P5528 | BEDSIDE
Direct acting oral anticoagulants are more effective than Vitamin-K-antagonists for the resolution of established left atrial thrombi in patients with atrial fibrillation

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Background: Left atrial appendage thrombus formation (LAAT) occurs in a relevant subset of patients with atrial fibrillation (AF), despite oral anticoagulation (OAC) with Vitamin K antagonists (VKA). LAAT is associated with a 5-fold increased risk in stroke. The objective of this study was to assess resolution rates of LAAT if treated with direct acting OAC (DOAC) in a patient cohort with therapeutic failure of VKA.
Methods and results: In this prospective registry 37 patients (age 73.7±8.2 years, CHADS2 2.5±1.1, 62% male) were enrolled with LAAT despite VKA treatment. The patients had a high prevalence of ischemic or non-ischemic cardiomyopathy with a reduced left ventricular ejection fraction (LVEF) of 43.4±17.1% and increased LV-enddiastolic volumes (LVEDV, 160.4±63.0ml), including 32% of patients with LVEF <35%. Echocardiography confirmed a so called "thrombogenic milieu" in all patients with spontaneous echo contrast grading >2 iand reduced LAA peak emptying velocities (23±13cm/s). Mean LAAT width and length was determined with 0.9±0.4 and1.5±0.7cm. In a first step all patients received intensified VKA therapy with targeted INR ranging between 2.5-3.5 for six weeks. In cases with persistent LAAT after this follow-up (FU) period, alternative therapeutic options were discussed with the patient, and if consenting, VKA was switched to DOAC (n=18) with dabigatran (n=5), rivaroxaban (n=8), or apixaban (n=5). FU was performed after six and 12 weeks under DOAC treatment including clinical examination and transesophageal echocardiography (TEE).Overall VKA showed a poor capability for midterm thrombus resolution after six weeks of intensified anticoagulant treatment. We identified only three cases (8.1%) with LAAT disappearance, and one patient experienced massive LAAT expansion (2.7%). After switching anticoagulant treatment to DOAC, LAAT resolution was observed in 11 out of 18 patients (61%), including six patients out of eight, which were treated with rivaroxaban (75%), three out of five under anticoagulant therapy with dabigatran (60%), and in three out of five patients under apixaban (60%). When comparing the absolute LAAT resolution rates of VKA (8.1%) with DOAC (61%), this difference reached statistical significance ($p<0.05$). We observed no major bleeding complication during FU in patients treated with either VKA or DOAC.
Conclusion: These preliminary results of a single-centre registry give interesting insights in promising characteristics of all three so far available DOACs. These substances might enable effective anticoagulant treatment of patients with therapeutic failure of VKA therapy.

P5529 | BENCH
Rivaroxaban inhibits angiotensin II-induced cardiac fibrosis via reduction of inflammatory cytokines production through the growth stimulating signal pathway

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Purpose: It is known that the proliferation and migration of cardiac fibroblasts (CFs) lead to cardiac fibrosis which is deeply associated with cardiac remodeling cause heart failure. Recently, factor Xa (FXa)-dependent protease-activated receptor (PAR)-1 and PAR-2 cleavage has been reported play a role in tissue fibrosis and remodeling. However, there has been few evidence to substantiate the pleiotropic effects of direct FXa inhibitor. In this study, we aimed to investigate whether treatment of rivaroxaban, which is an oral approved direct FXa inhibitor, attenuates cell proliferation and migration in angiotensin (Ang) II induced mice CFs.
Materials and methods: Confluent fibroblasts derived from myocardium of mice were cultured with or without rivaroxaban of various concentrations for 3 hours. Proliferation assays using MTT assay method and cell migration were performed after 24 hours of Ang II (10-8M) stimulation. Comprehensive cytokine and chemokine chemiluminescence reactions were evaluated by mouse cytokine array after 18 hours of Ang II stimulation. Tissue inhibitor of metalloproteinase (TIMP)-1 production was also measured by ELISA after 24 hours of stimulation. The signal pathways were evaluated using the signal pathway reporter assay and dual luciferase assay.

Results: After Ang II stimulation, rivaroxaban inhibited cell proliferation by 72.5% in 0.01 μg/ml, 95.1% in 0.1 μg/ml, 85.0% in 1 μg/ml and 77.5% in 5 μg/ml, respectively. Cell migration was decreased by 73.4% in rivaroxaban induced cells. In mouse cytokine array measuring 40 cytokines, we observed various chemiluminescence reactions by Ang II stimulation, including Interleukin-16, TIMP-1 and tumor necrosis factor-α. The productions of those 3 cytokines were significantly reduced with rivaroxaban pretreatment. TIMP-1 production was decreased in rivaroxaban induced CFs in various concentrations (49% decrease in 0.01 μg/ml, 51% in 0.1 μg/ml, 55% in 1 μg/ml and 46% in 5 μg/ml). In dual reporter assay analysis, rivaroxaban also inhibited various inflammatory signal pathways, including nuclear factor-kappa B pathway, cyclic adenosine monophosphate pathway and mitogen-activated protein kinase pathway.
Conclusions: These data suggest that rivaroxaban inhibits proliferation and migration of CFs via reductions of various major inflammatory signal cascades involved in cardiac fibrosis.

THROMBOSIS AND ANTITHROMBOTIC THERAPY: MISCELLANEOUS

P5531 | BEDSIDE
A study of platelet inhibition, using a "point of care" platelet function test, following primary percutaneous coronary intervention for ST-elevation myocardial infarction (PINPOINT-PPCI)

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Background: Bivalirudin and prasugrel are well recognized for their efficacy in the treatment of ST-elevation myocardial infarction (STEMI) but their use in combination has not been well tested. Bivalirudin has a superior bleeding profile compared to heparin but is associated with a higher rate of acute stent thrombosis (ST). We aimed to test whether potent oral anti-platelet therapy provides early protection against ST.
Methods: The study of platelet inhibition, using a 'point of care' platelet function test, following primary percutaneous coronary intervention for st-elevation myocardial infarction (PINPOINT-PPCI) trial (ISRCTN82257414) enrolled 108 patients presenting with STEMI treated with pre-procedural oral loading of Prasugrel 60mg & peri-procedural Bivalirudin (as per the HORIZONS-AMI protocol, stopping the infusion at the end of the procedure). Patients underwent Multiplate platelet function testing (adenosine diphosphate (ADP), aspirin & thrombin assays) on arrival at hospital, at the completion of the procedure, 1, 2 and 24hours post-procedure, with measurement of thromboxane receptor function at baseline & 24hours. In-hospital and 30-day major adverse cardiac event (MACE) rates, bleeding and stent thrombosis events were recorded.
Results: Radial access was used in 101 patients (93.5%) with a median door to procedure end time of 54.6 mins [interquartile range (IQR) 40.2, 70.2] and a median bivalirudin infusion duration of 30 mins [IQR 19.8, 42.0]. Patients demonstrated high baseline platelet reactivity, with a mean baseline ADP-induced platelet aggregation of 888.9±332.8 AU*min. The median change in ADP activity during the procedure was -139 AU*min [IQR -357, 8]. Immediately post-procedure, 75.5% patients demonstrated high residual platelet reactivity (HRPR; ADP >468 AU*min). At 2hours HRPR persisted in 24.3%. Five patients suffered in-hospital MACE (4.6%); all events were ST (4 acute). All acute ST occurred <120mins after the index procedure and were associated with HRPR. No overt evidence of bleeding was detected, one individual was observed to drop their haemoglobin >4g/dL but did not require any treatment.
Conclusion: Combination therapy with bivalirudin and prasugrel provides low rates of MACE with no observed bleeding. However, pre-procedural loading of a potent oral antiplatelet therapy does not prevent the occurrence of acute ST. HRPR was observed in all patients with acute ST and persisted in 24.3% of the entire cohort 2hours post-procedure.

P5532 | BENCH
Pleiotropic effects of statins in coagulability

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Background: Statins are potent lipid-lowering drugs. Statins have also been proven to have anti-thrombotic effect and can prevent thrombosis. However, the mechanism underlying the clinically beneficial effects of statins in reducing thrombus formation and anti-coagulation remain to be established. We thus conduct this study to investigate the potential mechanism.
Methods and results: We first conducted in vitro studies. Human hepatoma cells (HepG2) were cultured and stimulated with simvastatin 10μM for different time intervals (2hrs, 6hrs, 12hrs, and 24hrs). We found simvastatin increased the expressions of protein C after 2hrs (361±64%, p<0.01) and 6hrs of stimulation (313±59%, p<0.01). In the in vivo study, Wistar rats were fed with pure water (control) or simvastatin (5 mg kg^{-1} d^{-1}) for 1 week and 2 week. The serum protein C levels were increased in the simvastatin group (7±2.2 unit/ml (control), 23.4±19.3 unit/ml (1 week) and 23.4±18.2 unit/ml (2 weeks), respectively). Regarding the possible mechanism of simvastatin induced protein C expression, we found that the level of hepatocyte nuclear factor (HNF) was also increased in the HepG2 cells stimulated with simvastatin and in the rat fed with simvastatin. The human protein C gene promoter was cloned into the luciferase reporter. We found that the protein C promoter activity was increased by simvastatin, and this effect was inhibited by HNF knockdown and constitutively active Rac1. (Control: 100±24%; simvastatin 2hrs: 361±64%; simvastatin 2hrs in HNF knockdown cells: 184±33%; simvastatin 2hrs in Rac V12 cells: 195±43%).
Conclusions: Stains may modulate protein C expression through Rac 1 and HNF. The pleiotropic anti-thrombotic effect of stains provide the rationale of using statins in the treatment of clinical conditions associated with thrombus formation, e.g., embolic stroke in patients with atrial fibrillation.

P5533 | BEDSIDE
Association of cyclooxygenase-1 gene C50T polymorphism with adverse cardiovascular events development in patients with ischemic heart disease, long taking acetylsalicylic acid

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The purpose - to study the prevalence of C50T allelic variants in the PTGS1 gene and its association with clinical presentation, biochemical, and functional markers of aspirin resistance (AR) in patients with ischemic heart disease (IHD).
Materials and methods: 173 patients with chronic IHD (stable angina, myocardial infarction) were examined. Standard therapy included ACE inhibitors, statins, beta-blockers and acetylsalicylic acid (ASA) at a dose of 75-100 mg was appointed. The control group included 28 healthy individuals of the same age as studied group. The follow-up period lasted for 34,5±1,2 months. At the retrospective analysis, 20 patients with adverse cardiovascular events (ACVE) in history (cardiovascular death, non-fatal acute myocardial infarction, ischemic stroke, unstable angina, urgent revascularization) considered as aspirin resistant patients and 153 patients without ACVE considered as aspirin sensitive. The level of 11-dehydro-thromboxane B2 in urine as a criterion for biochemical AR was determined by ELISA. Functional AR was identified by ADP- and arachidonic acid-induced light transmittance aggregometry. Genotyping was performed using polymerase chain reaction followed by restriction fragment length analysis.
Results: In the patient group the frequency of individual genotypes was: 86,7% with wild CC genotype; 12,7% - heterozygous genotype CT, and 1 patient (0,6%) - mutant genotype TT. Distribution of genotypes in the control group was as follows: CC – 85,7%, CT – 14,3%, mutant homozygotes have not been identified. No statistically significant difference of C and T alleles frequency between studied and control groups (p>0,05) was found. The total index of arachidonic acid-induced platelet aggregation in T-allele patients was not only significantly higher than that of the C-allele patients (p=0,001), but also it was higher than 20%. This is the criterion for functional AR. There were no statistically significant difference in ADP-induced aggregation and the urine 11-dehydro-thromboxane B2 level between patients with CC and (CT+TT) genotypes. The probability of ACVE developing for mutant T-allele patients was significantly higher (Odds ratio= 3,39; 95% CI [1,39-8,77], p=0,019), than for C-allele patients.
Conclusions: Mutant T allele in the PTGS1 gene was associated with functional AR in patients with IHD. The risk of adverse cardiovascular events was enhanced for T-allele patients with IHD on prolonged ASA therapy.

P5534 | BEDSIDE
Onset of antiplatelet action with high (100 mg) vs standard (60 mg) loading dose of prasugrel in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Purpose: In patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) a suboptimal degree of platelet inhibition for the first 2 hours following the standard 60 mg loading (LD) of prasugrel has been described.
Methods: In a prospective, 3-center, nonrandomized controlled study and following screening of 241 cases, 2 sequential groups of P2Y12 inhibitor-naive consecutive patients were loaded with either 100 mg (n=47) or 60 mg (n=35) of prasugrel. Platelet reactivity (PR) was assessed by VerifyNow at Hour 0, 0.5, 1, 2 and 4.
Results: At Hour 2, the primary endpoint of PR (in PRU) was marginally lower [least squares estimates mean difference (95%CI), -45.4 (-91.5 to 0.7), p=0.054], while PR % inhibition (median, first to third quartile) was higher [75.5% (24% to 91.8%) vs 23.5% (0% to 78.3%), p=0.02] in the 100mg compared to 60 mg LD group. At hour 2, prasugrel 100 mg over 60 mg LD significantly reduced high PR rates from 28.5% to 8.5% (>230 PRU threshold; p=0.035) and from 31.4%

to 10.6% (>208 PRU threshold; p=0.025), while resulted in lower rate of ≤20% platelet inhibition (23.4% vs 51.4%; p=0.01).
Conclusions: In STEMI patients treated with primary PCI a higher (100 mg) than the standard LD of prasugrel results in earlier, greater and more consistent platelet inhibition.

P5535 | BEDSIDE
Impact on clinical outcome of high/low on-clopidogrel platelet reactivity according to concordant platelet function tests

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Objectives: To evaluate the impact of high and low on-clopidogrel platelet reactivity (HPR/LPR) on clinical outcome according to the number of concordant platelet function tests (PFT).
Methods: HPR and LPR were prospectively identified in 624 patients exposed to a maintenance dose of aspirin and clopidogrel for at least 7 days having at least 2 different PFT techniques performed simultaneously. HPR and LPR were defined as VASP PRI ≥50% / <15%, P2Y12 reaction units (PRU) ≥208 / <86 (VerifyNowP2Y12 assay) or a residual platelet aggregation (RPA) ≥46.2% / <10% (light transmission aggregometry), respectively. The primary composite end point of all-cause mortality, non-fatal myocardial infarction, stent thrombosis, sudden cardiac death, urgent revascularization, and stroke was analyzed according to agreement between PFT. Bleeding complications were categorized according to BARC.
Results: Mean follow up on-treatment was 476±325 days. HPR was identified in 278 (45%) patients of whom 142 (23%) according to one PFT only, 86 (14%) and 50 (8%) according to two and three PFT, respectively. Independent predictors of HPR, defined as at least one positive PFT, were diabetes status and carriage of the loss-of-function allele CYP2C19*2. The primary endpoint occurred in 3.8% of the patients with good response as compared to 9.0% of the patients with HPR defined as at least one positive PFT (OR 2.53, 95% CI 1.27-5.05, p=0.007). There was a stepwise increase in the rate of the primary endpoint according to the number of PFT demonstrating HPR (7.7% vs. 7.0% vs. 16.0% according to 1, 2 and 3 concordant tests, respectively, p for trend = 0.0054). The presence of 3 concordant tests remained independently associated with the occurrence of the primary endpoint during follow up after multiple adjustments (adjusted OR 3.62, CI 1.49-8.81). The primary safety endpoint did not differ significantly according to LPR status and according to the number of PFT demonstrating LPR.
Conclusions: Multiple testing may reflect better the complexity of platelet function, improving the specificity of HPR and prediction of future cardiovascular ischemic events. This finding should deserve consideration in future clinical trials of personalized antiplatelet therapy.

P5536 | BEDSIDE
Incidence and predictors of thrombus inside the guiding catheter. an optical coherence tomography study

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Purpose: Optical coherence tomography (OCT) is a high-resolution intracoronary imaging technique able to identify thrombus. We sough to detect the incidence of thrombus inside the guiding catheter by OCT and its relationship with clinical and procedural factors.
Methods: Consecutive patients who underwent OCT pullbacks in our institution were screened. Only patients with visible guiding catheter on the pullback were finally included and divided into thrombus or no-thrombus group, according to presence of thrombus inside the guiding catheter. Clinical and procedural data, as well as in-hospital adverse clinical events related to thrombus were also recorded (acute myocardial infarction, cardiac death and intra-stent thrombosis).
Results: Out of 77 patients screened, 35 patients had visible guiding catheter on OCT pullback and were finally included: 21 patients (60%) had thrombus inside guiding catheter (thrombus group) and the remaining 14 (40%) did not (no-thrombus group). Patients within thrombus group were preferentially males (100% vs. 71%, p=0.05), admitted for acute coronary syndrome (76% vs. 36% p=0.02) and received more frequently percutaneous coronary intervention (86% vs. 43% p=0.01) as compared to no-thrombus group. On the other hand, in the no-trhombus group, OCT was performed more frequently for follow-up assessment compared to the other group (50% vs. 9%, p=0.008). No in-hospital clinical events related to thrombus were observed.
Overall heparin dose administered at the time of procedure was the same between the two groups. A second dose of heparin was administered more frequently in thrombus than in no-thrombus group (86% vs. 50%; p=0.01). Time between first heparin administration and OCT pullback (41[28-57] vs. 20 minutes [10-32], p=0.001), time elapsed from second heparin administration and OCT pullback (29 [19-48] vs. 16 minutes [12-22] p=0.002) and total procedural time (47 [36-69] vs. 31 minutes [26-39] p=0.005) were longer in thrombus compared to no-thrombus group. At multivariate analysis, total procedural time and time lag between the first heparin administration and OCT pullback were only predictors of thrombus inside the guiding catheter (HR 0.6 [0.37-0.96], p=0.03 and HR 1.9 [1.1-3.2], p=0.02, respectively).
Conclusions: Thrombus inside guiding catheter by OCT may be a frequent finding especially in long interventional procedure. Future studies are warranted to determine its clinical impact.

P5537 | BEDSIDE
Impact of dabigatran and phenprocoumon on ADP induced platelet aggregation in patients with atrial fibrillation (The Dabi-ADP-1 trial)

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Background: Thrombin plays a major role in hemostasis through fibrin formation as well as platelet activation and aggregation. Both low and high on-treatment platelet reactivity are associated with adverse clinical events. The impact of the direct thrombin inhibitor dabigatran etexilate on platelet function in patients in need of oral anticoagulation is unknown.
Methods: The "Impact of DABIgatran and phenprocoumon on the ADP induced platelet aggregation in patients with atrial fibrillation" (DABI ADP 1) study was a randomized trial performed at Deutsches Herzzentrum Munich, Germany, which enrolled patients with atrial fibrillation and an indication for oral anticoagulation. Concomitant therapy with P2Y12 receptor inhibitors was a key exclusion criterion. Patients were randomly assigned to receive either dabigatran (n=35) or the vitamin K antagonist phenprocoumon (n=35) for a 2 week period. The primary endpoint was ADP-induced platelet aggregation (in AU x min) assessed with multiple electrode platelet aggregometry at 14 days after randomization.
Results: There was no significant difference regarding the primary endpoint between both groups, dabigatran 846 [650 - 983] AU x min and phenprocoumon 839 [665 -1038] AU x min, p=0.90. Furthermore, no significant differences wer e observed regarding the secondary endpoints, ADPhs- (P=0.96), TRAP- (P=0.45) and COL- (P=0.55) induced platelet aggregation at 14 days. There was no death, myocardial infarction, TIMI major or minor bleeding during the study period.
Conclusion: Dabigatran as compared to phenprocoumon has no impact on the ex vivo- measured platelet reactivity in patients with atrial fibrillation
ClinicalTrials.gov identifier: NCT01339819.

P5538 | BEDSIDE
Insulin resistance affects pharmacodynamic profiles in patients with stable coronary artery disease treated with dual antiplatelet therapy

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Background: Although postprandial hyperglycemia may affect profiles of platelet reactivity through multiple mechanisms, whether or not insulin resistance (IR) contributes to differences of platelet reactivity profiles following hyperglycemia remains poorly explored.
Objectives: To investigate the impact of IR on platelet reactivity profiles in patients with stable coronary artery disease (CAD) who are treated with standard dual antiplatelet therapy.
Methods: A 75g oral glucose tolerance test was performed in 70 stable CAD patients treated with maintenance aspirin (100mg/day) and clopidogrel (75mg/day) therapy. Blood samples were collected before and 1 and 2 hours after glucose load. The degree of IR was estimated by the homeostasis model assessment (HOMA) according to standard definitions (HOMA-IR ≥2.5). Maximum platelet aggregation was assessed by light transmittance aggregometry using 5 and 20μmol/L ADP stimuli.
Results: There were 15 (21%) subjects who had IR. Following a glucose load, profiles of platelet reactivity varied according to IR status (Figure). In particular, following 20μmol/L ADP stimuli, there were with minimal changes over time in patient with IR (p for trend = 0.79), while there was a significant reduction in the non-IR group of patients (p for trend <0.001). Consistent findings were observed following 5μmol/L ADP stimuli. After adjustment for baseline platelet reactivity, there were significant differences in profiles of platelet reactivity according IR status (Fig. 1).
Conclusions: In patients with stable CAD who are treated with standard dual

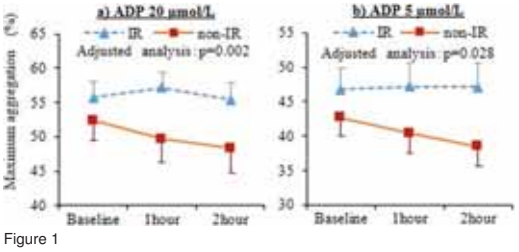

Figure 1

antiplatelet therapy, the presence of IR is associated with variations in pharmacodynamic response profiles following hyperglycemia.

P5539 | BEDSIDE
Efficacy of aspirin in aspirin-based versus non-aspirin based RCTs in the secondary prevention of MI: can we skip aspirin?

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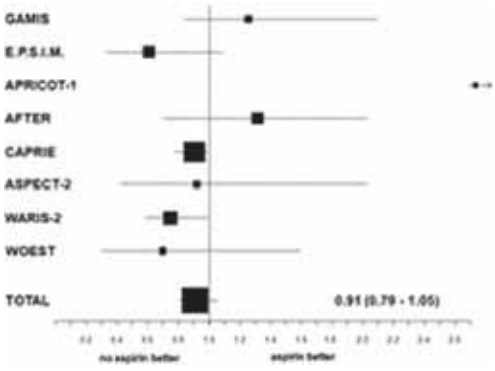
Background: Aspirin prevents reinfarction. Several newer and more effective antithrombotic therapies have been added on top of aspirin. They show, however, significantly increased bleeding, but have not been extensively tested without background aspirin.
Methods: We summarized results of the RCTs of aspirin versus antithrombotic therapy without aspirin in the secondary prevention of MI, carried out in 18,464 patients in 8 trials between 1980 and 2013.
Results: Reinfarction was seen in 4.4% on aspirin versus 4.1% on non-aspirin based therapy (OR 0.91, 95% CI 0.79 - 1.05 p=0.20, figure), whereas major bleeds occurred in 242/12,961 pts (1.9%) on aspirin versus 284/12,972 pts (2.2%) on non-aspirin based therapy (OR 1.10, 95% CI 0.99 - 1.40, p=0.06). When warfarin was the non-aspirin based comparator, reinfarction was seen in 223/3,131 pts (7.1%) on aspirin versus 201/3,122 pts (6.4%) on non-aspirin based therapy (OR 0.91, 95% CI 0.78 - 1.05, p=0.20), whereas major bleeds occurred in 60/3,131 pts (1.9%) on aspirin versus 134/3,122 pts (4.3%) on non-aspirin based therapy (OR 2.30, 95% CI 1.67 - 3.16, p=0.00001). When clopidogrel was the non-aspirin based comparator, reinfarction was seen in 187/6,127 pts (3.1%) on aspirin versus 172/6,084 pts (2.8%) on non-aspirin based therapy (OR 0.92, 95% CI 0.74 - 1.15, p=0.46), whereas major bleeds occurred in 182/9,830 pts (1.9%) on aspirin versus 150/9,850 pts (1.5%) on non-aspirin based therapy (OR 0.82, 95% CI 0.66 – 1.03, p=0.07).



Conclusion: In the secondary prevention of MI antithrombotic treatments without aspirin are at least as effective as those with aspirin strongly suggesting that aspirin can be skipped when other antithrombotic strategies are applied. This may lead to less bleeding, but only when clopidogrel is used.

P5540 | BENCH
Comparison of blood loss reducing efficacy of the antifibrinolytics tranexamic acid and aprotinine in a canine model of cardiopulmonary bypass

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Purpose: Anti-haemorrhagic drugs are being used to prevent and treat haemorrhagic complications in cardiac surgery. The serine-protease-inhibitor aprotinin is an antifibrinolytic agent that had been used in clinical practice for decades. In 2008, the BART-study revealed its unfavourable effects on postoperative mortality, which led to its withdrawal from the market. Today, the lysine-analogue tranexamic acid (TA) is available for the clinical routine. We compared the effects of aprotinin and TA on postoperative blood loss, hemodynamic, hemostaseologic and inflammatory parameters, using a canine model of cardiopulmonary bypass (CPB).
Methods: Beagle dogs were randomized into three groups (n=8/group). Control dogs received placebo, treated groups were given aprotinin or TA. All animals received heparin and underwent 90min of CPB. The weaning from the heart-lung-machine was followed by administration of protamine and 130min of observation. We regularly determined blood loss and coagulation parameters, while hemodynamic parameters were continuously monitored. To assess the systemic inflammatory response induced by CPB, plasma levels of IL-6, IL-8 and TNF-α were determined by ELISA.
Results: Compared to control, aprotinin significantly reduced blood loss (105±22ml vs. 41±8ml), while TA was found to be less effective (65±16ml). Regarding hemodynamic and coagulation parameters, no significant difference was detected among the groups. The elevation of proinflammatory cytokine levels during CPB was tendentially decreased by aprotinin, while a significant anti-inflammatory effect was observed in the TA group (TNF-α 90min after starting CPB: 5.2±1.2ng/ml control vs. 3.7±0.9ng/ml aprotinin vs. 0.8±0.3ng/ml TA).
Conclusions: Compared to aprotinin, TA is less effective in reducing blood loss, but has a stronger anti-inflammatory effect. Our work points out the need for the development of novel pharmacological tools for effective and safe postoperative blood loss reduction.

P5541 | BEDSIDE
Fixed-dose aspirin-clopidogrel combination enhances compliance to aspirin after acute coronary syndrome

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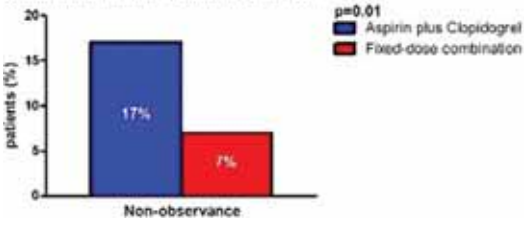
Purpose: The purpose of this retrospective study was to compare observance with antiplatelet therapy in stented ACS patients treated with the same doses of aspirin and clopidogrel administered in the FDC form or separately.
Methods: Consecutive patients admitted to our institution for ACS were considered eligible if they had undergone successful stent implantation and demonstrated good in-hospital response to aspirin. Biological assessment criterion for aspirin good-response is arachidonic acid–induced aggregation (AA-Ag)≤30%. To avoid any observance issue due to association with the daily 75 mg dose of clopidogrel, a daily 75 mg dose of nonenteric-coated aspirin was administered under nurse control. Aspirin response was re-evaluated on day 3. Patients with AA-Ag>30% before discharge were considered as poor responders and excluded from study. Patients were treated at discharge with an antiplatelet therapy using 75mg doses of aspirin and clopidogrel administered separately (A+C) or in the FDC form. At one month clinical follow up, patients with AA-Ag>30% were considered as non-observant. The primary endpoint was detection of a difference in treatment observance between the FDC and A+C groups.
Results: Between 2011 and 2013, a total of 390 patients were enrolled in study including 106 in the FDC group and 284 in the A+C group. (table1) At the time of discharge, 10 patients in the A+C group were classified as aspirin resistant and excluded. No significant difference between the two cohorts was reported. At one month the non observance rate was 7% (n=7) in the FDC group versus 17% (n=49) in the A+C group (OR [95%CI]: 0.32 [0.14–0.74]; p=0.01).

Figure 1. Impact of aspirin and clopidogrel administered separately or in a fixed-dose combination form on therapeutic non-observance.



Conclusion: A fixed combination of aspirin clopidogrel significantly improves drug observance, crucial end point after a stented ACS.

P5542 | BENCH
Compound 21, a selective angiotensin II type 2 receptor agonist, downregulates LPS-stimulated tissue factor expression in human peripheral blood mononuclear cells

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Purpose: Intricate interrelationships connect Tissue Factor (TF), the principal initiator of the clotting cascade, to inflammation, a cross-talk amplified by locally active angiotensin (ang) II, a proinflammatory agent with direct TF stimulating properties mediated by the ang II type1 receptor (AT1R)s. However, ang II also stimulates ang II type 2 receptor (AT2R)s and they may as well contribute to TF expression. We investigated the effect of C21, a specific AT2R agonist, on TF antigen (ag), TF mRNA and TF procoagulant activity (PCA) in peripheral blood mononuclear cell (PBMC)s activated by LPS, a pro-inflammatory and procoagulant stimulus.
Methods: PBMCs were obtained from healthy volunteers through a discontinuous Ficoll/Hystopaque density gradient. C21, PD123319, a selective AT2R antagonist, and Olmesartan (OLM), a selective AT1R antagonist were added at log-increasing steps to LPS-activated PBMCs. PCA was assessed by a 1-stage clotting assay. TFag expression was assessed by ELISA. Levels of TF mRNA were assessed by real-time polymerase chain reaction.
Results: LPS increased TFag expression (from 26±18 pg/mL to 832±288 pg/mL, n=39, $p<0.001$) and stimulated PCA (from 0.01±0.008 to 1.12±0.2 AU, n=67, $p<0.001$) and TF mRNA (from 0.004±0.0009 to 0.82±0.57 normalized fold expression, n=5 each, $p<0.001$). C21 downregulated in a concentration-dependent manner TFag and PCA (TFag: 10^{-8}M: -34±27%, 10^{-7} M: -37±15%, 10^{-6}M: -44±17%, 10^{-5}M: -44±20%, n=14, $p<0.001$; PCA: 10^{-8}M: -26±25%, 10^{-7}M: -40±22%, 10^{-6}M: -42±19%, 10^{-5}M: -40±27%, n=14, $p<0.001$), an effect antagonized by PD123,319 (10^{-6}M) (TFag: 10^{-8}M: -10±18%, 10^{-7}M: 0±25%, 10^{-6}M:

-0±24%, 10^{-5}M: -3±21%, n=6; PCA: 10^{-8}M: -2±46%, 10^{-7}M: -22±15%, 10^{-6}M: -11±42%, 10^{-5}M: -16±13%, n=14) and left unchanged by OLM (10^{-6}M). C21 blunted LPS-induced TF mRNA (from 0.82±0.57 to 0.24±0.13 normalized fold expression, n=5 each, p<0.001), a 3.5-fold inhibition. PD123,319 per se did not affect LPS induced TFag expression and PCA in the 10^{-8}–10^{-6} M range, as opposed to the highly significant inhibition exerted by OLM. The effect of OLM, was preserved in the presence of PD123,319. BAY 11-7082, a specific NFκB inhibitor, abolished at a 10^{-5}M concentration LPS-induced PCA.
Conclusions: C21, a selective AT2R agonist downregulates the transcriptional expression of TF in LPS-activated PBMCs, a finding consistent with the existence in PBMCs of AT2Rs whose stimulation attenuates inflammation-mediated procoagulant responses. The data open insofar unexplored and potentially relevant facets to our understanding of the complex links connecting ang II to inflammation and coagulation.

ACUTE CORONARY SYNDROME: COMORBIDITIES AND PROGNOSIS

P5544 | BEDSIDE
Is GRACE risk score a useful tool to predict stroke after an acute coronary syndrome?

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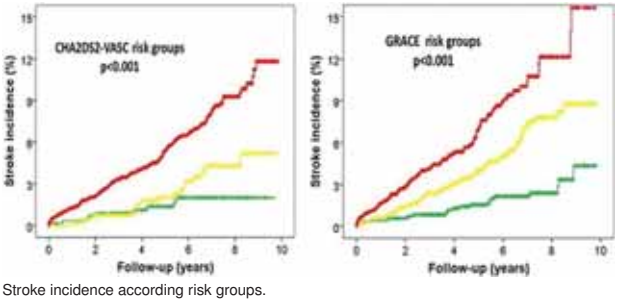
Background: The risk of stroke after an acute coronary syndrome (ACS) is increased. The aim of this study was to do a comparative validation of 6-month GRACE risk score and CH2DS2VASc score to predict the risk of post-ACS stroke.
Methods: This is a retrospective study carried out in a single center with 4,229 ACS patients discharged from 2004 to 2010 (66.9±11.8 years, 27.9% women, 64.2% underwent PCI). The primary endpoint of this study was the occurrence of an ischemic stroke during follow-up (median 4.6 years, IQR 2.7-7.1 years). Cumulative stroke rates were analyzed by the method of Kaplan-Meier for the different risk groups, evaluating hazard ratios with a Cox Analysis. We also calculated the discrimination and the predictive values of both scores. The risk reclassification was analized with Pencina's method
Results: 184 (4.4%) patients developed an ischemic stroke; 153 (83.2%) had sinus rhytm and 31 (16.9%) has atrial fibrillation. The HR for CHA2DS2VASc was 1.36 (CI 95% 1.27-1.48, p<0.001) and for GRACE was 1.02 (CI 95%, 1.01-1.03, p<0.001). Both risk scores shown adequate discriminative ability (c-statistcs 0.63±0.02 for CHA2DS2VASc, and 0.60±0.02 for GRACE). By reclassification method there was not difference between GRACE and CHA2DS2VASc risks scores (NRI 1.98%, p=0.69). Comparing moderate-high risk patients with low risk patients, both risk scores showed very high negative predictive value (98.5% for CHA2DS2VASc, 98.1% for GRACE). The sensitivity of CHA2DS2VASc was higher than GRACE risk score (95.1% versus 87.0%), whereas specificity was lower (14.4% versus 30.2%).



Stroke incidence according risk groups.

Conclusions: GRACE risk score has a discrimination and a negative predictive value similar than CHA2DS2VASc to predictive post ACS stroke. In this way, our study shows a new utility for GRACE risk score.

P5545 | BENCH
Decreased levels of circulating natural regulatory T cells after ST-segment elevation myocardial infarction

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Background: Contribution of natural regulatory T cells (Treg) to the pathogenesis of acute myocardial infarction (MI) remains elusive. Treg cells are thought to play a protective role in atherosclerosis, and, in concert with this notion, previous reports demonstrated decreased levels of Treg cells in the course of ST-segment elevation MI (STEMI). However, much less is known whether alterations of Treg cell numbers could persist for longer periods of time.
Aim: To investigate whether levels of natural Treg cells are subject to long-term quantitative changes within first months following STEMI.
Methods and results: A flow-cytometric analysis of frequencies of natural Treg cells delineated by CD4+CD25+CD127- phenotype in eighteen patients (mean age 65±12 years, 55% males) at the time of admission for the first STEMI and after four to six months was performed. All patients were successfully treated with primary percutaneous coronary intervention. At the time of MI, natural Treg cells comprised 10.66% [7.42-13.69] of all CD4+ T cell population. Quite surprisingly, after six months, the frequencies of CD4+CD25+CD127- T cells significantly decreased and reached the level of 6.16% [5.22-8.07] (p<0.0001). Consistently, at four to six months following STEMI, significant decrease in mean fluorescence intensity of CD25 expression on circulating CD4+ T cells was found (p=0.0003).

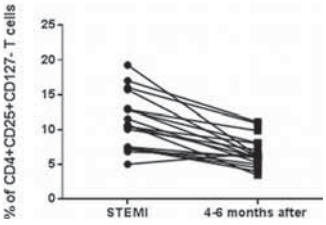

Figure 1

Conclusions: The recovery from STEMI is associated with the decrease in numbers of putatively protective Treg cells.

P5546 | BEDSIDE
How reliable is the EKG in detecting stent thrombosis after successful primary PCI in acute ST elevation myocardial infarction

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Purpose: Stent thrombosis (ST) is one of the most feared complications of PCI presenting as recurrent acute myocardial infarction sometimes leading to cardiogenic shock, life-threatening arrhythmias or sudden death. We sought to determine the sensitivity, specificity and the predictive value of EKG alone, and EKG in combination with clinical evaluation, for diagnosis of suspected ST.
Methods: We retrospectively reviewed the records of patients who presented with STEMI to our hospital between Jan 1, 2007 and Dec 31, 2012. Records of patients who had urgent repeat coronary angiography within 30 days of the index primary PCI for STEMI were analyzed. EKG's done just prior to the urgent angiography were reviewed without knowledge of the presenting symptoms or the results of the repeat angiogram. We also reviewed the medical records of these patients to see if ST was being considered by the treating cardiologist.
Results: A total of 963 STEMI patients underwent primary PCI with stent implantation, of which 44 (4.57%) had repeat urgent coronary angiography within 30 days. The age range was 43-86 years (mean 62.6 yrs. ±10.2), with 68% males. Of these 44 patients, 19 patients had ST on angiogram. EKG was suggestive of ST in 17/44 patients but only 12 were found to have ST on angiogram. EKG was not suggestive of ST in the other 27/44 patients, yet 7 of these patients were found to have ST. Combined EKG and clinical evaluation was suggestive of ST in 26/44, of which 18 patients had ST on angiogram, and the combination did not suggest ST in 18/44 patients, of which only 1 patient had ST on angiogram. The sensitivity, specificity and predictive values of the above diagnostic tools are detailed in Table 1.

Table 1

Diagnostic tool	Senstivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
EKG alone	63.2% (38.4–83.7)	80.0% (59.3–93.1)	70.6% (44.0–89.6)	74.1% (53.7–88.8)
Combined EKG and clinical evaluation	94.7% (73.9–99.1)	68.0% (46.5–85.0)	69.2% (48.2–85.6%)	94.4% (72.6–99.0)

PPV: positive predicitive value; NPV: negative predicitive value.

Conclusion: Although EKG remains an important tool to diagnose ST, it missed ST in almost one third of our patients. Combining EKG and clinical evaluation improved the sensitivity and negative predictive value at the cost of specificity. We suggest that even in the absence of significant EKG changes, a high index of clinical suspicion for ST should lead to emergent coronary angiography, as significant proportion of these patients will be found to have ST.

P5547 | BEDSIDE

Impact of occluded culprit arteries on the long-term outcomes of patients with non-ST-elevation myocardial infarction. Could they be true STEMI-equivalents?

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Background: Recent studies have suggested that a subset of patients with non-ST-elevation myocardial infarction (NSTEMI) who had occluded culprit arteries had worse outcomes compared to those with non-occluded culprit arteries. Therefore, they have been regarded as "STEMI-equivalents". We aimed to compare the clinical characteristics and the long-term prognosis between these "STEMI-equivalents" and STEMI patients.
Methods: A total 5025 patients with acute MI from 9 centers of 2 universities were retrospectively registered in COREA-AMI (Convergent REgistry of catholic and chonnAm university for Acute MI) registry. Out of these, the patients who had a total occlusion (TIMI 0 or I) of "culprit" left anterior descending artery (LAD) on the baseline angiography were selected as study subjects. They were classified into two groups by initial eletrocardiographic findings: the "NSTEMI" group (n=253) and the "STEMI" group (n=800). The clinical, angiographic findings and the incidences of adverse events including in-hospital death (IHD), cardiac death (CD), recurrent nonfatal MI (RMI), and target vessel revascularization (TVR) were compared between two groups. The median follow-up duration was 47.3 months (IQR 32.7–66.2).
Results: Patients in the STEMI group were younger and had lower left ventricular ejection fraction (LVEF). The peak levels of CK-MB and cardiac troponin were significantly higher in the STEMI group. Meanwhile, the NSTEMI group had more complex angiographic lesion (B2/C), multi-vessel disease, and smaller stent-diameter. The incidence of IHD was significantly higher in the STEMI group than in the NSTEMI group (4.1% vs 1.2%, p=0.027). In the multivariate logistic regression, age (adjusted HR 1.161, 95% CI [1.104-1.221], p=0.035), LVEF (0.938 [0.894-0.985], p=0.010), and peak level of troponin (1.102 [1.100-1.104], p=0.016) were revealed as the independent predictors for IHD. During the 48-month follow-up, however, CD (10.6% vs 9.1%), RMI (6.3% vs 7.9%), and TVR (4.5% vs 3.2%) occurred at similar rates in both groups (all $p>0.05$). Furthermore, in the 12-month landmark analysis, the risk of all adverse events was not significantly different between both groups beyond 12 months ($p>0.05$).
Conclusions: Patients with NSTEMI who had an occluded "culprit" LAD demonstrated the similar rates of adverse cardiovascular events during 48 months, compared to the patients with STEMI. These patients in the NSTEMI group may represent true "STEMI-equivalents". Thus, the precise early risk stratification followed by an early intervention should be considered for these high risk patients.

P5548 | BEDSIDE

Is the obesity paradox present in the extreme Body Mass Index groups of patients with Acute Coronary Syndrome? Data from a national registry

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Background: In the general population, obesity has an important prognostic impact. However, in patients with cardiovascular disease it is described a paradoxical effect of obesity, in which patients with overweight and obesity have a better outcome. Some authors also describe a U-shaped risk, with the more extreme groups of Body Mass Index (BMI) having the worst outcome. However, these extreme groups are difficult to analyse due to the under-representation in study samples.
Objective: It was our objective to analyse in a large population of patients included in a national registry of Acute Coronary Syndromes the impact of BMI in prognosis, including the extreme groups.
Methods: From the 37.476 patients included in the registry, 32.300 had information on BMI and they were divided in five groups: Low-weight (BMI <18.8 kg/m^2), Normal (18.8 – 25 kg/m^2); Overweight (25 – 29 kg/m^2), Obesity (30 – 34 kg/m^2) and Severe Obesity ($\geq$35 kg/m^2). Study objective was the occurrence of in-hospital and 6-month death in the follow-up.
Results: Mean age was 65$\pm$13 years, 72% males and 43.5% had a ST-segment elevation myocardial infarction. In our sample, 0.6% had Low-weight, 27.2% Normal, 40.6% Overweight, 14.2% Obesity and 3.7% Severe Obesity. In-hospital mortality was 4.2%, and it decreases linearly with BMI increase, but with a small increase in the Severe Obesity group (8.9%, 5.4%, 3.7%, 3.3% and 3.8%, $p<0.001$). Major bleeding also decreases linearly (3.3%, 1.5%, 1.2%, 1.1% and 0.9%, p=0.004). For hospital mortality, only diabetes showed a significant interaction with BMI groups (p-value for the interaction = 0.040). In multivariate regression analysis and compared with the Normal group, only the Overweight group showed a lower risk of hospital mortality (OR 0.84, 95% CI 0.72 – 0.97, p=0.019). For major bleeding, no group had a significantly higher risk compared to the Normal group. In the follow-up, 6-month mortality was higher in the Low-weight group and was progressively lower with BMI increase (Log-rank, $p<0.001$). No interaction was found for gender, diabetes, age or ST-elevation myocardial infarction. In multivariate analysis, only the Obesity group showed a trend for lower 6-month mortality risk (HR 0.86, 95% CI 0.73 – 1.00, p=0.056).
Conclusions: Hospital and 6-month mortality is higher in Low-weight and Normal BMI groups, confirming the obesity paradox described previously. No significant increase was present in Severe Obesity group. On short- and medium-term, Overweight and Obesity group had the lowest risk of mortality, compared to the Normal group.

P5549 | BEDSIDE

Re-infarction in ST-elevation and non-ST-elevation acute myocardial infarction: are they different?

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Purpose: Re-Infarction (Re-AMI) can be a terrible complication in acute myocardial infarction (AMI). The rapid identification and management of patients in risk of developing Re-AMI could be associated with a better prognosis in AMI. The objective of this work was to identify and compare the predictors of Re-AMI in ST-elevation (STEMI) and in non-ST-elevation AMI (NSTEMI).
Methods: We studied 6900 patients with AMI in a multicentric registry: 3179 (46,1%) had STEMI and 3721 (53,9%) had NSTEMI. For the identification of Re-AMI predictors, we evaluated by multivariate analysis the following parameters: age, gender, cardiovascular and non-cardiovascular co-morbidities, Killip-Kimball class at admission, performance of coronary angiography, coronary anatomy, ejection fraction (EF) and pharmacological in-hospital treatment.
Results: Overall, the presence of Re-AMI was found in 99 (1,4%) patients with AMI and was more prevalent in NSTEMI (67 patients – 1,8%) than in STEMI (32 patients – 1,0%), p=0,006. In both groups Re-AMI was an independent predictor of in-hospital mortality [STEMI - OR: 4,78 (1,07 to 21,2), p=0,04 and NSTEMI – OR: 11,67 (2,92 to 46,51), $p<0,001$]. By multivariate analysis, left main stenosis $>50\%$ and EF $<50\%$ were identified as independent predictors of Re-AMI in both groups. We identified some specific predictors of Re-AMI according to the type of AMI. In STEMI the presence of in-hospital treatment with IIb/IIIa glycoprotein inhibitors [OR: 2,96 (1,27 – 6,86), p=0,01] was identified as an independent predictor of Re-AMI. In NSTEMI, age [OR: 1,05 (1,02 – 1,08), $p<0,001$] and previous peripheral arterial disease [OR: 3,27 (1,50 – 7,08), p=0,003] were identified as independent predictors of Re-AMI. On the other side, performance of coronary angiography appears to be a protective factor against development of Re-AMI in NSTEMI [OR: 0,22 (0,10 – 0,46), $p<0,001$].
Conclusions: Re-AMI is a rare complication in both STEMI and NSTEMI, although more prevalent in NSTEMI. Left main stenosis $>50\%$ and EF $<50\%$ were identified as predictors of Re-AMI in both in STEMI and NSTEMI. There are some specific predictors of Re-AMI according to the type of AMI.

P5550 | BENCH

Increasing the use of an early invasive strategy in acute coronary syndromes reduces reinfarction rates: an instrumental variable approach to administrative health data

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Purpose: An early invasive strategy compared to a conservative strategy in acute coronary syndrome (ACS) reduces mortality and myocardial infarctions in randomized trials. We investigated whether this benefit can be retrieved in an unselected population of ACS patients using instrumental variable (IV) analysis.
Methods: We identified all patients hospitalized with a first ACS in 2005–11 from the Danish national registries including data on the entire population of 5.5 mio. An early invasive strategy was defined as receiving a diagnostic coronary angiography within 3 days of admission. IV analysis was applied to address the inherent treatment selection bias of observational comparisons. An IV randomizes patients to a given treatment using a naturally occurring characteristic, e.g. place of residence, thus offsetting measured and unmeasured confounders and providing unbiased estimates of the treatment effect. We used quartiles of CAG rates in 29 hospital catchment areas as IV to estimate the effect of early versus conservative invasive strategies on mortality and reinfarctions at 60 days. We estimated absolute risk reductions (ARR), which in an IV context are interpreted as the effect of increasing the use an early invasive strategy in hospital catchment areas of the lower quartiles to that of higher quartiles.
Results: We included 52,615 patients. Our IV allocated patients with similar characteristics to different levels of treatment as required (Table). An early invasive strategy reduced reinfarctions with ARR: -10.8% (-13.9% to -7.7%; $p<0.001$)

Table 1. Characteristics according to IV

	Low quartile	2nd quartile	3rd quartile	High quartile
Age*	67 (58–77)	67 (57–77)	68 (58–78)	68 (58–78)
Females, %	35.6	37.5	36.7	35.4
Charlson comorbidity index^	0.5 (1.0)	0.5 (1.0)	0.5 (1.0)	0.5 (1.0)
CAG within 3 days, %	37.2	41.6	43.6	53.7
Revascularization within 3 days, %	30.2	32.7	35.1	42.9

*Median (interquartile range); ^Mean (standard deviation).

compared to a conservative invasive approach. Mortality was unchanged, ARR: -2.6% (-6.5% to 1.3%; p=0.20).
Conclusions: In unselected ACS patients, an early invasive strategy reduced reinfarctions at 60 days by almost 11% compared to a conservative strategy. No significant effect on mortality was found. Instrumental variable analysis is a promising analytical approach to administrative health data.

P5551 | BEDSIDE
The presence of in-hospital atrial fibrillation is associated with mortality in patients with chronic kidney disease complicated with acute myocardial infarction

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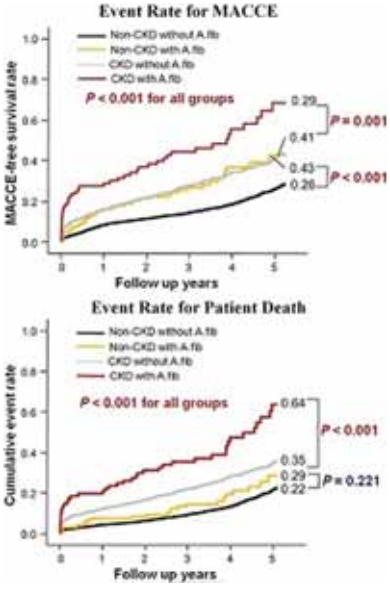
Purpose: Chronic kidney disease (CKD) is an important predictor for mortality after acute myocardial infarction (AMI). Atrial fibrillation (AF) often coexists with CKD and AMI. However, the impact of AF on mortality and morbidity in CKD patients complicated with AMI remains unclear.
Methods: A total of 4738 patients with AMI were consecutively enrolled between 2004 and 2009 from 9 hospitals. CKD was defined as eGFR <60 mL/min/1.73m^2. Patients were divided into CKD (n=1181) and non-CKD (n=3607) groups, and then were analyzed to investigate the association with mortality and morbidity according to presence of AF. The primary endpoint was a composite of MACCE including death from any cause, recurrent non-fatal MI, ischemic stroke or re-hospitalization for heart failure.
Results: The prevalence of in-hospital AF in CKD group was significantly higher than in non-CKD group (6.77% vs. 3.27%, $P<0.001$). During a mean follow-up period of 3.5±1.7 years, a total of 1107 (23.4%) composite MACCE occurred after the index PCI: 34.8% in CKD group, 19.6% in non-CKD group ($p<0.001$). In both CKD and non-CKD groups, the cumulative event rate of MACCE was significantly higher in patients with AF than in patients without AF at the 5-year follow-up (CKD: 68.5% vs. 41.2%, $p<0.001$, non-CKD: 42.7% vs. 26.2%; $p<0.001$). Especially, a presence of AF was independently associated with mortality in CKD group (adjusted HR, 1.87; 95% CI, 1.15-3.06; p=0.01), while not in non-CKD group (adjusted HR, 0.74; 95% CI, 0.34-1.64; p=0.16).



K-M cumulative event rate.

Conclusions: In AMI population, a presence of in-hospital AF was an independent predictor of composite of long-term MACCE in both CKD and non-CKD groups. Of note, a presence of AF was associated with increased mortality in CKD patients, while not in non-CKD patients.

P5552 | BEDSIDE
Circulating NT-proBNP in post ACS patients who remained asymptomatic and event free during 400 day follow-up

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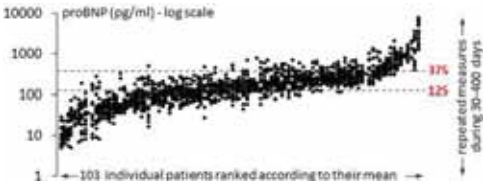
Background: Limited data are available on NT-proBNP and its evolution during one year follow-up in asymptomatic patients stabilised after acute coronary syndrome (ACS) admission.
Purpose: Describe 1-year NT-proBNP patterns in asymptomatic patients after ACS.
Methods: BIOMArCS is an observational study of ACS patients in 18 hospitals in our country Treatment is left to the discretion of the physician. During 1 year follow-up, 20 repeat blood samples are taken at preset time intervals. Serum and plasma are separated and stored on site at -80C within 2h, until batch analysis in the central laboratory of the Erasmus MC. This abstract describes 103 patients who remained free of death, ACS-readmission, revascularisation and angina until 400 days. We determined NT-proBNP with the Roche STAT on Cobas e system in their repeated samples.
Results: Mean age was 65 (SD 5) years, 79% were men, 64% had STE-ACS. Patient profile was typical for an ACS population. Discharge medication included antiplatelet therapy (99%) and statins (97%). Median peak NT-proBNP within 30 days was 568 (IQR 220 to 1195) pg/ml. During 30 to 400 days 1574 repeated blood samples were collected, with a median of 16 (IQR 15 to 17) for each patient. NT-proBNP >125 pg/ml (heart failure threshold in ESC guidelines) was observed in 50% of samples; levels $>3*125$ were found in 16% of samples (in 49% of patients). The within-patient variability explained 19% of total variation, and was much smaller than the between-patient variability (figure). Mean change in NT-proBNP between 30 and 400 days was -2.2 pg/ml.



Conclusions: Asymptomatic post-ACS patients have fairly stable NT-proBNP during 400 days, in a range that is compatible with heart failure according to ESC guidelines. Interpatient variability is substantial.

P5553 | BEDSIDE
In-hospital case-fatality and one-survival after acute myocardial infarction in Chile, 2002-2011: a national trends analysis

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Age-standardised myocardial infarction (MI) mortality rates have declined during the past decades in many countries. Part of this decline is due to an increase in survival. During the last decade a health care reform was implemented in Chile to provide effective preventive and curative services for priority health conditions, in which MI was included. Aim: to estimate trends in hospital case-fatality rates and long-term survival from MI in Chile between 2002 and 2011.
Methods: Population based study using person unique identification number linked hospital and mortality data. Data was obtained from the national Hospitalizations and Mortality Databases from the Ministry of Health, which covers 100% of hospitalizations (public and private) and deaths registered in Chile. International classification of disease codes I21-I22 were used to identify MI cases. All-cause mortality was the main outcome in this analysis. We estimated in-hospital case-fatality and one-year survival after discharge among all patients who were admitted to hospital due to a first MI in Chile. We used Kaplan-Meier method to estimate survival and Prais-Winsten (PW) regression to evaluate trends expressed as percentage change per year (IC 95%). Separate analyses of in-hospital case-fatality and one-year after discharge survival were done.
Results: During 2002-2012 a total of 65,225 fatal and nonfatal hospitalized first MI occurred (STEMI and non-STEMI). 31.4% were women. Women were significantly older than men (68.6±13.5 vs. 61.6±13.1y; $p<0.0001$). Vital status information at one-year was available for 92.4% of patients (there were no differences in age or sex between cases with and without vital status information). In-hospital case-fatality was reduced from 16.8% in 2002 to 10.0% in 2011. In-hospital survival increased at an average annual rate of 0.68 percentage points (IC95% 0.57-0.81) during this period. After discharge, one-year survival improved from 88.9% to 91.1% (PW: 0.23 percentage points/year; IC95% 0.14 to 0.33). In men, in-hospital case-fatality declined from 13.1% to 7.7% (PW: -0.52; IC95% -0.68 to -0.35) and one-year survival increased from 90.4% to 92.1% (PW: 0.19; IC95% 0.04 to 0.36). In women the corresponding values were 25.0% to 15.1% (PW:-1.04; IC95% -1.21 to -0.88) and 84.9% to 88.4% (PW: 0.31; IC95% 0.21 to 0.42) respectively.
Conclusions: Over the past decade, there has been an improvement in in-hospital case fatality and 1 year after discharge survival in patients hospitalized for a MI in Chile. These results are useful for the evaluation of public policies implemented during this period.

THROMBOSIS: BASIC MECHANISMS AND CLINICAL MANAGEMENT

P5555 | BENCH
Fibrinogen chain gene polymorphisms regulate fibrinogen, D-Dimers and factor V activity in patients with stable angina pectoris

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Purpose: Fibrinogen genetic variability plays a significant role in atherogenesis. However, the role of specific polymorphisms (rs1800790, rs2070011) remains unclear. We examined the combined effects these polymorphisms on the coagulation process and endothelial function in Caucasian subjects.
Methods: We enrolled 422 patients with coronary artery disease (CAD) and 277 controls. The rs1800790 (G455A) and the rs2070011 (G58A) polymorphisms were estimated by PCR and appropriate restriction enzymes (HaeIII and AciI respectively). Fibrinogen and D-Dimer levels, as well as factors (f) V, X activity were measured by standard coagulometry techniques. Flow-mediated dilation (FMD) was assessed by brachial ultrasound.
Results: 58AA subjects had lower fibrinogen levels in controls (p=0.038). Importantly, the 455AA homozygosity was associated with enhanced fibrinogen levels in both groups (p=0.035 controls and $p<0.001$ CAD). Both the 58AA (p=0.027) and 455AA homozygotes (p=0.022) had higher levels of D-Dimer in the CAD group. Interestingly, the 455AA homozygotes had increased fV activity in the CAD group (p=0.048). However, no significant effects were observed on fX activity and FMD. Further analysis revealed that fibrinogen levels were strongly associated with CAD (1.005 [1.003-1.007], $p<0.001$) as well as the presence of MI (1.003 [1.001-1.005], p=0.001). Similarly, D-Dimer levels were also strong predictors of CAD (1.001 [1.001-1.002], $p<0.001$), but not of MI (1.000 [1.001-1.001], p=0.083). When fV and fX activities were examined for potential associations with clinical manifestations, we found that fV activity was associated with increased number of diseased vessels (1.016 [1.001-1.030], p=0.037), while fX activity was strongly related to MI (0.985 [0.973-0.997], p=0.013).
Conclusion: The rs1800790 variant increases fibrinogen and D-Dimers levels as well as fV activity, therefore contributing to the initiation and progression of atherosclerosis. Also, we have shown that fibrinogen and D-Dimers levels were strong predictors of CAD and MI. Importantly, our results highlighted a new role for fV and fX regarding to the number of diseased vessels and the risk of MI respectively.

P5556 | BENCH
Differential regulation of tissue factor isoforms by microrna 181b

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Background: Inflammatory cytokines, such as tumor necrosis factor (TNF)-α, have been shown to alter the differential isoform expression as well as the biological functions of tissue factor (TF) in endothelial cells (ECs). The mechanism by which DNA Topoisomerase (Topo) I is regulated to enable alternative splicing of TF remains unclear. Here, we investigate the impact of micro (mi)RNAs on Topo I-regulated TF isoform expression and endothelial thrombogenicity.
Methods and results: Upon stimulation with TNF-α human dermal microvascular endothelial cells (HMEC-1) differentially expressed miR-181b and let-7b. Using mimics and antagonists for theses miRNAs prior to TNF-α treatment levels of asTF and flTF were determined by real-time PCR and Western blotting. Cellular procoagulant activity was analyzed by a chromogenic TF activity assay. Moreover, human myocardial biopsies of 118 patients were probed for miR-181b, Topo I and TF isoform expression.
Treatment with miR-181b increased the flTF/asTF ratio and raised the endothelial TF activity. The Topo I 3'UTR was identified as a target for miR-181b. Upon stimulation with TNF-α treatment of HMEC-1 with miR-181b led to a down regulation of Topo I expression. This was associated with a modulation of the serine/arginine-rich (SR) protein phosphorylation pattern.
In myocardial biopsies levels of TNF-α and Interleukin-6 mRNA positively correlated with miR-181b (n=108-110, $p<0.005$, $p<0.0001$). Increased miR-181b levels were associated with a higher flTF/asTF ratio (n=110, $p<0.0001$).
Conclusions: In this study, we showed for the first time that miR-181b modulated the differential isoform expression of TF as well as the endothelial thrombogenicity by directly regulating the expression of alternative splicing kinase Topo I.

P5557 | BEDSIDE
Evaluation of clinical risk factors to predict high on-treatment platelet reactivity and outcome in patients with stable coronary artery disease (PREDICT-STABLE)

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Purpose: The influence of clinical risk factors on high on-treatment platelet reactivity (HPR) in patients with stable CAD undergoing elective PCI has been poorly characterized. This study was designed to identify clinical risk factors that are easily available from patient data to predict HPR and 12 months major adverse events under treatment with aspirin and clopidogrel in patients undergoing non-urgent PCI.
Methods: 739 consecutive patients with stable CAD were recruited. On-treatment platelet aggregation was tested by light transmittance aggregometry. Major cardiovascular events (MACE) were recorded during one-year follow-up.
Results: Degree of on-treatment platelet aggregation was influenced by different clinical risk factors. In multivariate regression analysis older age, diabetes mellitus, elevated body mass index, renal function and left ventricular ejection fraction were independent predictors of HPR. After weighing these variables according to their estimates in multivariate regression model, we developed a score to predict HPR in stable CAD patients undergoing elective PCI (PREDICT-STABLE Score). Patients with a high score were significantly more likely to develop MACE within one year of follow-up. This association was confirmed in a validation cohort of 591 patients.
Conclusions: In conclusion, variability of on-treatment platelet function and associated outcome is mainly influenced by clinical risk variables. Identification of high risk patients (e.g. with high PREDICT-STABLE score) might help to identify risk groups that benefit from more intensified antiplatelet regimen. Additional clinical risk factor assessment rather than isolated platelet function-guided approaches should be investigated in future to evaluate personalized antiplatelet therapy in stable CAD-patients.

P5558 | BEDSIDE
The clinical characteristics and the risk of bleeding in atrial fibrillation patients receiving anti-platelet drugs: one-year follow-up of the Fushimi AF Registry

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Purpose: Oral anticoagulants (OAC) are effective in preventing stroke and thromboembolism in patients with atrial fibrillation (AF) and many AF patients have concomitant vascular diseases including coronary artery disease and peripheral artery disease. Therefore, they are often given the combination of OAC and anti-platelet drugs (APD), and are exposed to increased risk of bleeding. However, in the real-world clinical settings, the present status of anti-platelet therapy of Japanese AF patients is not clear.
Methods: The Fushimi AF Registry was designed to enroll all of the AF patients. We have enrolled 3,821 patients and one-year follow-up was completed in 2,966 patients from March 2011 to December 2013. We defined APD as aspirin, ticlopidine, clopidogrel and cilostazol. We investigated clinical characteristics of AF patients under APD and the incidence of bleeding at one-year follow-up.
Results: Of 2,966 patients, 901 patients (30.4% of all patients) were given APD and 137 patients (4.6% of all patients) were given multiple APDs. Among 901 patients under APD, 552 patients (61.3%) did not have coronary artery disease or peripheral artery disease. Among 137 patients under multiple APDs, 29 patients (21.2%) did not have coronary artery disease or peripheral artery disease. These data suggests overuse of APD in Japanese AF patients. At one-year follow-up, major bleeding occurred in 46 (1.55%) and minor bleeding occurred in 80 (2.70%). Of 137 patients under multiple APDs; 57 received OAC, and 80 received no OAC. Of 57 patients with multiple APDs plus OAC, major bleeding occurred in 1 (1.75%) and minor bleeding occurred in 4 (7.02%). Of 80 patients with multiple APDs and no OAC, major bleeding occurred in 3 (3.75%) and minor bleeding occurred in 1 (1.25%). In patients with OAC, the incidence of minor bleeding was higher in patients with multiple APDs plus OAC than with single or no APD plus OAC, although not statistically significant (7.02% vs. 2.98%; p=0.09). The incidence of major bleeding was similar between the two groups (1.75% vs. 1.46%; p=0.85). Of 57 patients with multiple APDs plus OAC, 13 patients had no vascular disease. In patients without OAC, the incidence of all bleeding was similar between patients with multiple APDs and those with single or no APD (5.00% vs. 3.79%; p=0.59).
Conclusion: Japanese AF patients receive multiple APDs without rational indication, suggesting the overuse of APD in the real-world clinical practice. The combination of APDs and OAC increases the risk of bleeding, and its necessity should be re-assessed.

P5559 | BEDSIDE
The current use of direct oral anticoagulants (DOACs) for the treatment of VTE in Europe-PREFER in VTE

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Purpose: The conventional treatment of venous thromboembolism (VTE) in Europe has been use of heparin and vitamin K antagonists (VKA), and although effective, they have numerous limitations. Direct oral anticoagulants (DOACs) are promising alternatives with the potential to overcome these limitations. All DOACs have shown similar efficacy as compared with heparins and VKA and they have a better safety profile. The PREFER registry is the first large study to investigate the management and the use of DOACs in VTE.
Methods: The PREFER registry has enrolled patients starting in January 2013 until March 2014. A total of 338 centres in France, Germany, Switzerland, Austria, Italy, Spain and UK (33.2% office-based and 66.7% hospital-based) are participating. We collect patient's characteristics and history as well as medical management information related to the VTE index event (pulmonary embolism (PE) and deep vein thrombosis (DVT)) at time of diagnosis, at baseline and at 1, 3, 6 and 12 months follow-up. We report the first data of the use of DOAC's. Enrolment in countries is ongoing.
Results: DOACs were used more frequently in younger patients (<65 years, 26.8%; 65-74 years, 19.8% and ≥75 years 14.3%), and were used less frequently in those with lower weight (≤60 kg vs >60kg; 13.4% vs 23.3%), renal insufficeny (22.7% vs 11.1% in patients with CRCL levels ≤60ml/min), diabetes (22.9% vs 13.5% in patients without/with diabetes), and those at risk of bleeding (HAS-BLED low 27.1%, medium 17.8%, high 12.5%). There was great variation in use related to region, which is related to the different time of approval of these agents. Use in PE patients was as frequent as use in DVT patients (Table1).

Table 1. Use of DOACS (percentage) for VTE by country, indication and inhibitor type

	France (N=248)	Germany/Austria/ Switzerland (N=565)	Italy (N=816)	Spain (N=199)	UK (N=15)	Total (N=1843)
Use of DOACs (mono or in combination)						
Overall VTE	91 (36.7%)	264 (46.7%)	26 (3.2%)	16 (8.0)	6 (40.0%)	403 (21.9%)
PE	55 (36.9%)	55 (43.7%)	8 (2.7%)	8 (7.5%)	–	126 (18.4%)
DVT	36 (36.4%)	209 (47.8%)	18 (3.5%)	8 (8.7%)	6 (50.0%)	277 (23.9%)

Conclusions: DOACs are used frequently throughout Europe for VTE treatment, but usage varies greatly from country to country and is also associated with patient characteristics.

P5560 | BEDSIDE
Triple antithrombotic therapy is not associated with long-term cardiovascular events and bleeding complications after drug-eluting stent implantation

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Triple antithrombotic therapy increases the risk of bleeding events in patients undergoing drug-eluting stent (DES) compared with dual anti-platelet therapy (DAPT). However, it is uncertain whether warfarin control is associated with reduced cardiovascular events and bleeding events in patients undergoing DES with triple antithrombotic therapy.
Methods: We investigated clinical outcomes in 1207 consecutive patients (82.8% men, mean age 67.0 years) of our institute PCI database between 2004 and 2011. Baseline clinical characteristics and MACCE and bleeding complication were compared between triple antithrombotic therapy and DAPT group. MACCE was defined as death, ACS, target vessel revascularization, and stroke.
Results: 95 (7.9%) patients received triple antithrombotic therapy. The comorbidities with hypertension (81.1%) and diabetes (54.7%) were more common in triple antithrombotic therapy. The mean INR at the time of PCI was 1.8. The target PT-INR levels was set between 1.6 and 2.5 and calculated the percent time in the therapeutic range (TTR). The median TTR was 78.4% (interquartile range, 67.4-87.6%). By Kaplan-Meier survival analysis, warfarin therapy was not associated with MACCE (P=0.98) and bleeding (P=0.74). Multivariable Cox regression analysis revealed that triple antithrombotic therapy was also not the independent predictor for the MACCE and bleeding (HR, 1.12; 95%CI, 0.76-1.73; P=0.58).
Conclusions: Triple antithrombotic therapy did not have a predictive value for the occurrence of MACCE and bleeding complications as long as warfarin was controlled tightly with lower INR value.

P5561 | SPOTLIGHT
Coffee reduces death risk after acute myocardial infarction: a meta-analysis

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Purpose: It has been shown that habitual coffee consumption is protective against coronary heart disease in women however it is not clear whether such cardio-protection is conferred upon those who have already experienced an acute myocardial infarction.
Methods: We conducted a dose-response meta-analysis of prospective studies which probed the relationship between coffee intake and mortality in those who had experienced an acute myocardial infarction. Using a defined-search strategy, electronic databases (MEDLINE and Embase) were searched for papers published between 1946 to July 2013. Two eligible studies that investigated post acute myocardial infarction mortality risk against coffee consumption were identified and appraised using set criteria. Combined, these studies recruited a total of 3,271 patients for which 604 deaths were observed. The hazard ratios for the following experimental groups were defined: Light coffee drinkers (1-2 cups/day) versus non-coffee drinkers, heavy coffee drinkers (>2 cups/day) versus non-coffee drinkers and heavy coffee drinkers versus light coffee drinkers.
Results: A statistically significant inverse correlation was observed between coffee drinking and mortality; all three groups demonstrated a significant reduction in relative risk. Light coffee drinkers versus non-coffee showed a risk ratio of 0.79 (95% confidence interval (CI)= 0.66-0.94, p=0.008); heavy coffee drinkers versus non-coffee drinkers showed a risk ratio of 0.54 (95% CI = 0.45–0.65, p=0.00001) and heavy coffee drinkers versus light coffee drinkers showed a risk ratio of 0.69 (95% CI = 0.58–0.83, p=0.0001)

Conclusions: Drinking coffee habitually following an acute myocardial infarction was associated with a reduced risk of mortality.

P5562 | BEDSIDE
Plaque debris embolization than thrombus embolization was the higher risk of slow flow in the patients with or without acute coronary syndrome during percutaneous coronary intervention

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Background: Slow flow or no re-flow phenomenon (slow/no flow) during coronary intervention is mainly caused by distal embolization of thrombus and plaque debris, and is associated with unfavorable long-term clinical outcomes. Slow/no flow occurs in both acute coronary syndrome (ACS) and non-ACS patients during percutaneous coronary intervention (PCI). However, the contribution of thrombus and plaque debris for slow/no flow was unknown. Therefore, we examined the association of thrombus and plaque debris embolization with slow/no flow.
Methods: Consecutive patients who received PCI with filter-type distal protection device (Filtrap) were prospectively enrolled (n=520, 291 ACS and 229 non-ACS patients) from August 2008 to May 2012. We evaluated the distal embolization of thrombus and plaque debris by the captured material in Filtrap. Filter slow/no flow was defined angiographically.
Results: Filter slow/no flow occurred more frequently in ACS than in non-ACS patients (36% vs. 17%, P<0.001). Distal embolization of plaque debris with or without thrombus was detected in 103 (35%) ACS and 42 (18%) non-ACS patients. Distal embolization of thrombus alone was detected in 161 (55%) ACS and 103 (45%) non-ACS patients. Filter slow/no flow occurred more frequently in the patients with plaque debris embolization than in the patients with thrombus embolization alone both among ACS (91% vs. 6%, p<0.001) and non-ACS (83% vs. 2%, p<0.001) patients groups.
Conclusion: Plaque debris embolization was the higher risk of slow/no flow compared with thrombus embolization both in ACS and non-ACS patients.

P5563 | BEDSIDE
Cardiac troponin I, NT-proBNP and galactin-3 are elevated in patients with unrecognized myocardial infarction detected by cardiac magnetic resonance imaging

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Purpose: To determine the association between levels of cardiac biomarkers and

an unrecognized myocardial infarction (UMI) in patients with suspected stable coronary artery disease (CAD) with or without significant stenosis in the coronary artery supplying the infarcted area.
Methods: A total of 234 patients (median age 65 years; 66% men) with suspected stable CAD without previously known myocardial infarction (MI) were examined with late gadolinium enhancement magnetic resonance imaging and coronary angiography. For each patient with an UMI, the status of the coronary branch supplying the infarcted area was independently determined; a stenosis grade ≥70% was regarded as significant. Blood samples were drawn at enrolment and high sensitivity cardiac troponin I (hs-cTnI) (Abbot), NT-proBNP (Roche) and Galectin-3 (bioMérieux) were analyzed.
Results: UMI was detected in 58 of the 234 patients (24.8%), 39 (67%) of the UMIs were located in an area supplied by a coronary branch with a significant stenosis. The median levels of hs-cTnI, NT-proBNP and Galectin-3 were higher in patients with UMI compared to those without: 5.4 vs. 3.7 ng/L ($p<0.001$); 172.5 vs. 93.5 ng/L (p=0.005); and 11.1 vs. 10.0 ng/L (p=0.028), respectively. There was no significant difference in levels of the biomarkers among UMI patients with or without significant stenosis in the coronary artery supplying the infarcted area (p=0.99; p=0.48; and p=0.22). There were significant correlations between the volume of the infarcted area and hs-cTnI (Rho= 0.40; p=0.002) and NT-proBNP (Rho= 0.41; p=0.001). In a linear regression model comprising presence of UMI, age and the degree of the most severe coronary stenosis, the level of hs-cTnI was independently associated with the presence of UMI (p=0.002). In corresponding models, neither NT-proBNP, nor Galectin-3, was independently associated with presence of UMI.
Conclusions: The levels of hs-cTnI, NT-proBNP and Galectin-3 were elevated in patients with UMI. The association between the hs-cTnI level and UMI was independent of age and degree of coronary stenosis.

P5564 | BEDSIDE
Measurement of inflammatory biomarkers soluble urokinase Plasminogen Activator Receptor and CRP before PCI improve risk prediction by GRACE risk score in patients with ST-segment myocardial infarction

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Purpose: Global Registry of Acute Coronary Events (GRACE) risk score is an established tool for assessing risk in patients with acute coronary syndrome (ACS) and has been validated for up to 5 years of follow-up. The inflammatory biomarkers soluble urokinase Plasminogen Activator Receptor (suPAR) and high sensitive C-reactive protein (CRP) are both independent predictors of outcome in ACS patients. We aimed at testing if adding these biomarkers to GRACE score would improve risk prediction in a population of patients treated with primary percutaneous intervention (pPCI) for ST-segment myocardial infarction (STEMI).
Methods: Amongst 730 consecutive patients admitted with STEMI for pPCI from September 2006 to December 2008 at a single high-volume invasive heart centre in Copenhagen, Denmark, 670 patients were eligible for this study. Plasma samples were obtained prior to pPCI and clinical variables were gathered at baseline and survival status and information on subsequent hospital admissions were obtained from national registers. Survival analysis for all-cause mortality was performed for the logarithmically transformed GRACE score, suPAR and CRP in the same Cox proportional hazards model, and improvement in Harrell's C statistics and continuous net reclassification was calculated for the addition of the biomarkers to GRACE score.
Results: During a median follow-up period of 5.0 years, 140 deaths (21%) were registered. Both biomarkers (hazard ratio [HR] per increase in standard deviation [SD] of log[suPAR] concentration: 1.43, 95% confidence interval [CI] 1.28-1.61; and HR per increase in SD of log[CRP]: 1.23, 95% CI 1.13-1.34) and GRACE score (HR per increase in SD of log[GRACE]: 2.14, 95% CI 1.79-2.56) were all highly significantly associated with mortality (all $P<0.0001$). Addition of suPAR and CRP to a model solely consisting of GRACE score improved the predictive accuracy for the outcome of all-cause mortality (C statistics from 0.741 to 0.792, $P<0.001$) and the net reclassification significantly (NRI 0.196, 95% CI 0.093-0.299, $P<0.001$). No interaction was found between levels of biomarker and Grace Score.
Conclusions: The inflammatory biomarkers suPAR and CRP obtained prior to pPCI improve prediction of all-cause mortality by GRACE score up to 5 years after STEMI.

VENTRICULAR FUNCTION AND HAEMODYNAMICS

P5566 | BENCH
Pulsatile venous-arterial perfusion using a novel synchronized cardiac assist device augments coronary artery blood flow during ventricular fibrillation

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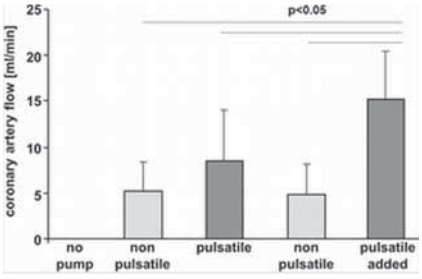
Patients with cardiogenic shock have a very high mortality. Here we report the first use of a percutaneous pulsatile cardiac assist device based on a novel control of a diagonal pump synchronized with the heart cycle by means of an ECG signal. Eight domestic pigs underwent mandatory ventilation. During sinus rhythm, there were no differences between pulsatile and non-pulsatile perfusion with regard to pulmonary artery pressure (PAP), pulmonary wedge pressure (PWP), central venous pressure (CVP), MAP (mean arterial pressure), mean pulse pressure and mean coronary artery flow (CAF). After 2 minutes of complete cardiac arrest (ventricular fibrillation), circulatory support with the i-cor® in venoarterial non-pulsatile ECMO mode (3l/min) restored systemic circulation with an increase of MAP to 78.3mmHg and CAF to 5.27ml/min. After changing from ECMO settings to pulsatile mode (3l/min, 75 bpm, pulse amplitude range 3.500rpm), MAP did not change significantly (75.6mmHg), however CAF increased to 8.45ml/min. After changing back to non-pulsatile mode, MAP remained stable (83.6mmHg) but CAF decreased to 4.85ml/min. Thereafter pulsatile cardiac assist was established with a reduced blood flow of 2.5l/min and the pulse amplitude range was extended to 4.500 rpm. Under these conditions, MAP remained stable (71.0mmHg) but CAF significantly increased to 15.2ml/min, $p<0.05$.



Conclusion: Percutaneous cardiac support using a VA cardiac assist equipped with a novel diagonal pump is able to restore and increase systemic and coronary circulation during ventricular fibrillation. ECG triggered synchronized cardiac assist provides an additional increase of coronary artery flow. These promising results are to be confirmed in humans.

P5567 | BEDSIDE
Evidence for impaired left ventricular mechanical efficiency during exertion in patients with HFPEF

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Purpose: Impaired diastolic reserve characterises heart failure with preserved ejection fraction (HFPEF). Although the presence of excess extracellular matrix has been presumed to be the fundamental mechanism, the potential contribution of other mechanisms affecting active and passive components of diastolic function have not been comprehensively assessed. In this study we investigated the role of altered myocardial energetics in the pathophysiology of HFPEF.
Methods: Patients with HFPEF, hypertension and healthy controls underwent simultaneous right-heart catheterisation, echocardiography and simultaneous arterial and coronary sinus blood gas sampling at rest and during supine-cycle ergometry.
Results: At peak exercise pulmonary capillary wedge pressure was markedly higher in HFPEF compared to healthy and hypertensive controls (33±3 vs 16±2 and 17±1 mmHg both $p<0.001$). Left ventricular work (LVW) was similar in all groups at baseline, however peak exercise LVW was significantly lower in HFPEF compared to controls and hypertensives (17±2 vs 31±2 and 31±4 kg-m/min $p<0.001$ and $p<0.01$ respectively). Despite lower workload, the transcardiac oxygen gradient did not differ at rest or during exertion across groups. In this context, ventricular mechanical efficiency calculated as the ratio of left ventricular work to the trans-myocardial oxygen gradient during exertion was markedly lower in HFPEF compared to control and hypertensive groups (12.1±1.7 vs 21.8±1.3 and 23.4±2.4 au, both $p<0.05$). Myocardial uptake gradients for glucose and lactate did not differ between groups.
Conclusions: These data demonstrate the presence of reduced ventricular mechanical efficiency during exertion in HFPEF patients suggesting the presence of fundamental changes in energetics. Further studies are required to characterize the mechanical and molecular basis of altered energy utilization in HFPEF.

P5568 | BEDSIDE
Survival in patients with cardiomyopathy and duchenne muscular dystrophy in use of an angiotensin-converting enzyme inhibitor and a beta-blocker during long-term follow-up

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Purpose: All Duchenne muscular dystrophy (DMD) patients in the middle of second decade of life display cardiomyopathy. One of the major problems for clinicians dealing with the cardiomyopathy of DMD patients is unsuccessful treatment since appearing of congestive heart failure symptoms.
Methods: A progressive long-term follow-up (from 6 up to 18 years) of 68 patients with DMD (all with verified mutations of dystrophin gene). Mean age in the start of follow-up was 8 years. Cardiac examination was made in all patients (ECG routine, ECG monitoring, ECHO, Doppler).
Result: During the follow-up, all the patients were found to have indications for the use of an ACE inhibitor (left ventricular dilatation or/and systolic dysfunction) and almost half of the children had those for the administration of a beta-blocker (rigid sinus tachycardia). Patients were divided in two groups: group I patients (n=35) received long-term courses of therapy with an ACE inhibitor (captopril in a dose of 0,5 mg/kg/day) and a beta-blocker (metoprolol by individually adjusting its dose). Despite recommendations, Group 2 patients (n=33) were not treated with the above drugs. Mortality in group I during the follow-up period was 37% (13 patients), in group II – 60% (20 patients). In group I mean death age was 21,15 years (standard deviation 2,70 years; mediana: 25 percentile – 17 years; 75 percentile – 19,5 years; moda – 18 years; mode frequency – 5; min age 17 years, max age 25 years). In group II mean death age was 18,25 years (standard deviation 1,55 years; mediana: 25 percentile – 20 years; 75 percentile – 23,5 years; moda – 20 years; mode frequency – 3; min age 16 years, max age 21 years). No significant difference were found in mean death age. The part of survived patients to the age of 21 years was significantly higher in group I than in group II: related frequency 0,77 (95% CI 0,5983...0,94) versus 0,39 (95% CI 0,19...0,5974).
Conclusion: Early started long-term treatment by angiotensin-converting enzyme inhibitor and a beta-blocker in patients with Duchenne muscular dystrophy significantly increased the part of survived patients to the age of 21 years

P5569 | BEDSIDE
Multiple sclerosis determines subclinical biventricular dysfunction

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Background: Multiple sclerosis (MS), debilitating disease involving primarily the central nervous system, represents the main cause of nontraumatic neurological invalidity in young adults. Involvement of the autonomous nervous system and the assumed autoimmune etiology may lead to cardiovascular dysfunction. Aim. To assess systolic left and right ventricular function, and vascular function, in newly diagnosed patients with MS with no immunomodulatory treatment, by comparison with treated MS, and with controls (matched for age, sex, and risk factors).
Methods: 90 subjects (35±10 years, 59 women) were studied: 30 patients with newly diagnosed MS (MS1); 30 patients with treated MS (MS2); and 30 control subjects. LV systolic function was assessed by 2D EF, 3D EF, 3D global longitudinal strain (3DGLS), 6 basal segments averaged systolic velocity (S'), and global longitudinal strain (GLS) by speckle tracking. RV systolic function was assessed by fractional area shortening (FAS), tricuspid annular systolic excursion (TAPSE), systolic pulmonary artery pressure (SPAP), RV myocardial performance index (RVMPI), and RV global strain (RVGS) by speckle tracking. Arterial stiffness was assessed by intima media-thickness, pulse wave velocity, and parameters of wave intensity; endothelial function by flow mediated dilation.
Results: Patients with MS had significantly affected left and right ventricular systolic function by comparison to controls, demonstrated by 2D and 3D echocardiography, with no differences between the two MS groups (MS1 vs. C: all $p<0.001$; MS2 vs. C: all $p<0.001$) (table). All parameters of arterial and endothelial function were similar.
Conclusion: Patients with MS, either treated or not, have subclinical biventricular systolic dysfunction with normal vascular function, suggesting an intrinsic myocardial impairment, probably mediated through neuronal impairment. Early diagnosis by 2D and 3D echocardiography might be important for initiating preventive actions.
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P5570 | BENCH
The effect of left ventricular hypertrophy and associated diastolic dysfunction on left ventricular remodeling and exercise capacity in a murine model of mitral regurgitation

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Introduction: Degenerative mitral regurgitation (MR) is often accompanied by left ventricular hypertrophy (LVH) and diastolic dysfunction. This study determined the contribution of LVH and associated diastolic dysfunction on LV remodeling and exercise capacity in rats with significant MR.
Method: LVH and diastolic dysfunction were created by suprarenal aortic constriction (SAC) in SD rats. To test the effect of LVH and diastolic dysfunction on LV remodeling and exercise capacity, the rats were divided into 3 groups [SAC+MR group=SAC followed by MR operation, MR group=laparotomy followed by MR operation, Control group]. MR was created by following method. A fine needle was introduced through LV apex under the guidance of transesophageal echocardiography and made a hole on posterior mitral leaflet. SAC was done at 2 weeks before MR formation in SAC+MR group. Serial echo exams and exercise test were performed at 2-week intervals. Hemodynamic and histological analysis was done at 10 weeks after MR formation.
Results: During the LVH and diastolic dysfunction experiment, LV wall thickness increased in LVH group compared to control group whereas LV EF and E/E' did not change. In hemodynamic analysis, LV EDP and the EDPVR slope were greater in LVH group than in control group. Next, when we compared LV remodeling and exercise capacity between above 3 groups, LV dilatation and exercise intolerance were developed first in SAC+MR group. However, MR group showed a catch-up of remodeling and exercise intolerance at 10 weeks after MR formation (LV end-systolic dimension at 10 weeks after MR formation, 4.33±0.26 vs. 6.50±0.40 vs. 6.59±1.38 mm for control vs. MR vs. SAC+MR, $P<0.05$; LV end-diastolic dimension, 7.68±0.15 vs. 10.48±0.46 vs. 10.20±1.26 mm, $P<0.05$; exercise duration, 765.3±130.1 vs. 487.8±49.0 vs. 434.0±80.3 seconds, $P<0.05$; no statistical differences between SAC+MR group and MR group by Tukey's post hoc analysis). In neurohormonal activity, the level of BNP was not different between 3 groups. However interstitial fibrosis is greater in SAC+MR compared with MR and control.
Conclusion: We successfully set up two small animal models of LVH accompanied with diastolic dysfunction and significant MR. LVH and associated diastolic dysfunction did not affect LV remodeling and exercise capacity over time in rats with significant MR. This result may emphasize timely correction of MR when indicated irrespective of LVH and associated diastolic dysfunction.

P5571 | BEDSIDE
The left ventricular response to dobutamine in patients after apical ballooning syndrome compared to male and female controls

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Background: The aetiology of apical ballooning syndrome (ABS) is poorly understood. At present, we know there is an association between stress and catecholamine excess as well as a female preponderance. We also know that dynamic left ventricular outflow tract (LVOT) or mid ventricular (MV) obstruction is often seen at presentation. It has been postulated that gender differences in left ventricular (LV) size, response to adrenergic stimulation and the consequent ventricular obstruction with high apical wall stress may be important in the aetiology of ABS. We sought to determine whether patients with prior ABS are more likely to develop LV obstruction in response to adrenergic stimulation compared to age-matched male and female controls.
Methods: We performed dobutamine stress echocardiography (DSE) in 20 patients (all women) at least 5 weeks after ABS and compared this with 15 female and 10 male age-matched controls. The dobutamine infusion was stopped at 20 mcg/kg/min or earlier if LVOT obstruction occurred.
Results: At rest, male controls had larger LV end diastolic diameters than both ABS patients and control females (46.3±4.1 cm, 43.8±5.1 cm, and 41.9±4.3 cm, respectively, p=0.08). The peak dobutamine dose was slightly lower in men (16.0±5.1 mcg/min) compared with women (18.7±3.5 mcg/min in controls, 19.0±3.1 mcg/min in ABS). At peak dobutamine, 9 (45%) of the ABS patients developed ventricular obstruction compared with 8 (53%) control females and 7 (70%) control males (p ns). Males had a similar post-dobutamine peak LVOT velocity of 3.2±1.6 m/s compared with control females (2.8±0.8 m/s, p=0.36) and ABS females (2.5±1.2 m/s, p=0.21).
Conclusion: Both male and female controls were as likely as ABS patients to develop dynamic LV obstruction in response to a fixed-dose dobutamine infusion. LV obstruction may still have a role in the aetiology of ABS, though it would have to be mediated by differential catecholamine release in response to stress and/or the LV apical response to stress.

Abstract P5569 – Table 1

	LV systolic function					RV systolic function and SPAP				
	2D EF (%)	3D EF (%)	S' (cm/s)	GLS (%)	3DGLS (%)	FAS (%)	TAPSE	RVMPI	RVGS (%)	SPAP (mmHg)
MS1	55±6	53±7	5.9±1.1	–19.5±2.6	–14.7±3.1	40.7±7.9	22.7±2.2	0.6±0.1	–22.1±3.5	22±8
MS2	56±5	52±6	6.0±1.2	–20.2±1.8	–13.3±1.5	44.6±6.7	23.0±2.5	0.6±0.1	–22.8±3.1	27±12
Controls	66±6	64±2	7.3±0.9	–22.6±1.8	–20.3±1.8	53.1±8.9	26.3±2.7	0.4±0.1	–25.8±4.0	15±6

P5572 | BEDSIDE

Ventilatory inefficiency, diastolic dysfunction, mitral regurgitation and pulmonary hypertension during exercise: the culprit interaction in heart failure reduced ejection fraction

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Background: Dyspnea and exercise intolerance are landmark manifestations of heart failure (HF). An impaired efficiency in ventilation (VE) as indicated by a steep increase in VE vs CO2 output during exercise provides remarkable prognostic indications. We aimed at defining the role of different hemodynamic components that may determine the most unfavorable ventilatory phenotype and worse clinical status.
Methods: 71 HF reduced ejection fraction patients (mean age 67±11; male 72%; ischemic etiology 61%; NYHA class I, II, III and IV 13%, 36%, 39% and 12%, mean ejection fraction 33±9%) underwent cardiopulmonary exercise test evaluation on tiltable cycle-ergometer combined with simultaneous echocardiographic assessment.
Results: Patients were divided in 4 ventilatory classes (VC) according to the VE/VCO2 slope classification focusing on peak exercise variables. We observed a VC related increase in E/e' ratio, mitral regurgitation and pulmonary artery systolic pressure and a progressive reduction in TAPSE and peak VO2. The best correlation with VC groups was found for E/e' ratio and peak VO2.

Table 1

Peak exercise variables	VC I (n=23)	VC II (n=18)	VC III (n=21)	VC IV (n=9)	P coeff. Anova
Mitral regurgitation ≥3/4+, %	30	44	62	67	0.05
Rest E/e', ratio	18±9	28±13	30±15	32±10	0.006
Tricuspid annular systolic excursion (TAPSE), mm	22±4	20±4	18±6	18±3	0.05
Pulmonary artery systolic pressure, mmHg	51±15	61±16	64±24	65±17	0.04
Cardiac output, l/min	8.3±3	6.6±2	5.8±2	5.2±2	0.002
Cardiac power output, Watt	1.9±0.6	1.6±0.6	1.3±0.6	1.1±0.5	0.001
Oxygen consumption (VO_2), ml/kg/min	14.8±3.1	13±2.4	12.3±3.6	8.9±2	0.000

Conclusions: A remarkable culprit interaction emerged between the degree of diastolic dysfunction, mitral regurgitation, pulmonary hypertension and right heart dysfunction with inefficient VE during exercise. A systematic analysis of these hemodynamic determinants by stress echo combined with gas exchange analysis may become a valuable addition for appropriately refining therapeutic interventions.

P5573 | BEDSIDE

Longer interdialytic interval deteriorates systolic cardiac reserve, not resting Frank-Starling mechanism in maintenance hemodyalisis patients

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Purpose: Although cardiovascular events are the most frequent on the day after long (2-day) interdialytic interval in hemodialysis patients, the mechanism remains unclear. This study aimed to test the hypothesis that long interdialytic interval compromises systolic cardiac functional reserve.
Methods: Eighty patients on maintenance hemodialysis underwent three echocardiograms; just after hemodialysis, after short (1-day) and long interdialytic intervals. End-systolic elastance [Ees]) and arterial elastance [Ea] were measured using a noninvasive single beat technique. Ventricular-arterial coupling (VAC) was calculated as Ea/Ees. These measurements were repeated with 2 minutes hand-grip stress.
Results: As interdialytic interval became longer, there were increases in resting end-diastolic volume index (EDVI: 41±2 ml/m^2 just after hemodialysis, 52±2 at short interval, and 57±2 at long) and stroke volume index (SVI: 25±1 ml/m^2 just after, 34±1 at short, and 37±1 at long). However, LV diastolic function parameters (E/e' ratio and LA volume index) were also similar after long interval compared with those after short. Although Ees remained constant (p=0.951), Ea and VAC decreased similarly after short and long interdialytic interval, with VAC<1.0 at highest. At hand-grip stress, there were no significant differences in blood pressure increase among three conditions (p=0.308). However, there was a decrease in SVI and a less increase in stroke work only after long interdialytic interval (Fig. 1).

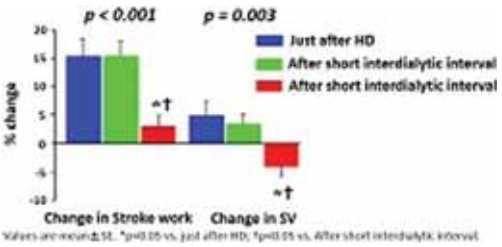

Figure 1. Comparisons of cardiac reserve.

Conclusions: Even after the long interdialytic interval, the Frank-Starling mechanism was still preserved at rest and VAC was similar to that with a short interval. However, cardiac systolic reserve during isometric stress significantly deteriorated only after a long interdialytic interval.

P5574 | BEDSIDE

Clinical and echocardiographic correlates of serum zinc levels in patients with acute and chronic heart failure

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Purpose: Zinc (Zn), the second most abundant trace element in the body, is involved in gene expression, cell growth and differentiation as a catalytic and structural cofactor. It is implicated in the antioxidant defense and regulation of various metalloproteases associated with the healing process. Emerging evidence suggests a pathophysiological role of micronutrient dyshomeostasis in heart failure, including promotion of adverse remodeling and clinical deterioration. We sought to evaluate serum Zn levels in acute (AHF) and chronic (CHF) heart failure.
Methods: We studied 125 patients, 71% male, aged 69±11 years, 37% with preserved left ventricular ejection fraction (LVEF ≥40%), including 81 with AHF and 44 with CHF; 21 healthy volunteers served as controls. Serum Zn levels were determined using air–acetylene flame atomic absorption spectrophotometry.
Results: Serum Zn was significantly lower in AHF and CHF patients compared to controls (AHF vs. controls, B= -15.752, 95%CI: -24.260 to -7.245, p<0.001; CHF vs. controls, B= -11.065, 95%CI: -21.560 to -0.570, p=0.039) after adjusting for age, gender, hypertension, diabetes, smoking, chronic obstructive pulmonary disease, coronary artery disease and atrial fibrillation. Moreover, serum Zn was significantly lower in AHF than in CHF (AHF vs. CHF, B= -8.670, 95%CI: -15.593 to -1.747, p=0.015) after adjusting for the above variables. Severe NYHA (p=0.004) was associated with lower serum Zn and serum albumin (r: 0.351, p<0.001) showed a positive association with serum Zn. On the other hand the ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/e') (r: -0.349, p=0.001), NT-proBNP (r: -0.297, p=0.004), CRP (r: -0.186, p=0.039), urea (r: -0.224, p: 0.016) and cTnTMAX (r: -0.336, p<0.001) were negatively correlated with serum Zn. In multiple linear regression, only NYHA class (B= -11.105, 95%CI: -16.740 to -5.469, p<0.001) and E/e' ratio (B= -1.093, 95%CI: -2.009 to -0.177, p=0.020) were independent predictors of serum Zn.
Conclusions: Serum Zn was decreased both in AHF and CHF patients compared to controls and seems to be lower in AHF vs. CHF. Furthermore serum Zn was independently predicted by clinical status and LV diastolic function.

P5575 | BEDSIDE

The severity of functional mitral regurgitation unlocks peculiar cardiopulmonary and echocardiographic phenotypes in heart failure

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Background: In heart failure (HF) the severity of mitral regurgitation (MR) at rest has a well established prognostic value and an increase in valvular regurgitation during exercise further adds to an increased risk. In cases of no or trivial MR at rest and comparable LV systolic function is unknown how dynamic MR vs

Abstract P5575 – Table 1

Variables	Group A (n=26)		Group B (n=30)		Group C (n=24)		P (A vs B)		P (B vs C)	
	Rest	Peak	Rest	Peak	Rest	Peak	Rest	Peak	Rest	Peak
LV ejection fraction, %	37±8	39±12	31±9	33±9	32±9	33±8	0.02	0.02	NS	NS
LV end diastolic volume indexed, ml/m^2	81±26	–	94±27	–	113±30	–	0.09	–	0.02	–
TAPSE, mm	18±5	22±5	19±3	21±4	15±4	16±5	NS	NS	0.00	0.00
PASP, mmHg	33±18	55±25	31±8	56±13	49±16	68±14	NS	NS	0.00	0.00
Workload, Watt	–	72±25	–	69±26	–	55±18	–	NS	–	0.04
Peak oxygen consumption (VO_2) ml O_2 kg^{-1} min^{-1}	–	14±4	–	13.2±3.6	–	12±3	–	NS	–	NS
O_2 pulse, ml/beat	–	10.1±2.4	–	8.8±2.5	–	8.2±3.1	–	0.05	–	NS

no dynamic MR may impact on cardiopulmonary and echocardiographic related phenotypes.
Methods: 80 HF patients (age 65±12; male 75%; ischemic etiology 67%; NYHA class I, II, III and IV 20, 36, 34, 10) with reduced ejection fraction (LVEF 33±9%) underwent cardiopulmonary exercise test (CPET) on tiltable cycle-ergometer (standard incremental ramp protocol) combined with exercise-echocardiography. The population was studied according to the degree of functional MR.
Results: Population was divided into three groups according to functional MR: Group A (rest MR≤1/4+, no dynamic MR), GroupB (rest MR≤1/4+, dynamic MR) and Group C (rest MR ≥3/4+). The latter population was taken as control group and well defined had higher resting and peak exercise pulmonary pressure and impaired right ventricular (RV) function. Interestingly, Group B patients exhibited a worsening pattern of exercise response (lower peak VO2, O2 pulse and workload) and more advanced cardiac remodeling compared to Group A (Table) despite similar LVEF, and exercise was the key physiological tool to unlock the worse clinical condition.
Conclusions: In HF patients the severity of rest functional MR is associated with the most unfavorable RV performance and pulmonary hemodynamic response. Among patients without significant MR at rest, development of dynamic MR translates into a worse exercise phenotypes and very likely more rapid clinical deterioration.

P5576 | BEDSIDE
Myocardial ventricular adaptation to pulmonary hypertension in non-ischemic dilated cardiomyopathy: a study performed by cardiac magnetic resonance

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Pulmonary hypertension (PH) is a prognostic factor in heart failure (HF) in terms of increased mortality and hospitalization. The prognostic impact of PH in HF suggests an important role for preclinical detection of signs indicating an ongoing RV dysfunction due to its remodeling. Several studies highlighted the utility of cardiac magnetic resonance (CMR) in patients with arterial pulmonary hypertension after discovering the presence of late gadolinium enhancement (LE) in the RV junctional insertion point of the interventricular septum. The aims were to evaluate the presence of junctional LE in patient with non-ischemic dilated cardiomyopathy (NIDC), to evaluate the relationship between this specific LE pattern and hemodynamics,to evaluate its prognostic role.
Methods: All consecutive patients admitted to our clinic with diagnosis of NIDC. All subjects underwent a diagnostic work-up including CMR and cardiac catheterization. On the follow-up, the events collected were:hospitalization for HF, cardiac death/transplantation and ventricular arrhythmias. Histological data of dead patients were collected.
Results: 118patients fulfilling the enrollment criteria. 38 patients (32%) showed junctional LE: in 29patients, junctional LGE was associated with midwall septal stria, in 8 LGE was confined only to the junctions points, and 1 had junctional LGE associated with a stria on free LV wall. In the junctional LGE group, the patients had increased RVEDV (p=0.03) and reduced RVEF (p<0.01). Patients with junctional LGE showed a worse hemodynamic profile in terms of PH (p=0.03) and LVEDP (p=0.02); moreover, this group showed an increased value of PCWP (p=0.02) with a mean value of 20mmHg indicating a post-capillary PH. During a follow-up of 37 months Kaplan Meier analysis revealed a correlation between junctional LE and occurrence of episodes of HF (p=0.03). On univariate analysis, all right catheterization parameters indicating a worse hemodynamics,including RV dysfunction, were associated with junctional LE. On multivariable analysis,only the increased LVEDP showed a trend for prediction of HF (p=0.079).
Conclusions: Junctional LE in the RV insertion points is a frequent CMR finding in NIDC, up to 32% in our population. The strictly relationship with all hemodynamic parameters indicating the presence of PH complicating the NIDC with junctional LE makes this peculiar pattern not specific for pre-capillary PH as herein demonstrated. The junctional LE pattern on follow-up was able to identify the patients at risk for developing HF, assuming the role of an imaging marker of ventricular remodeling in NIDC complicated by PH.

P5577 | BEDSIDE
Peak systolic ejection rate: a measure of left ventricular contractility determined on cardiac computed tomography

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Left ventricular ejection fraction (LVEF) is commonly used parameter of systolic function. However, it has limited value as an index of cardiac contractility. We aimed at feasibility of determination of the peak systolic ejection rate (PER) by means of multidetector computed tomography (MDCT) in a cohort of patients referred for a CT coronary angiography.
Data from 394 pts were analyzed retrospectively. There were 82 patients with normal coronaries and cardiac function and "zero" coronary calcium (controls, aged 50±9ys) and 312 with CAD (63±10ys), including 26 with ischemic heart failure (HF), 185 with chronic stable CAD (CAD) and 101 with previous CABG (CABG). Analysis of LV function included determination of the end-diastolic volume (LVEDV, ml), ejection fraction (LVEF,%), mass (LVM,g). LV volume changes were measured in 10 phases (1/10th of cardiac cycle) from 0% to 90%. Maximal change from neighbour phases relating to systole defined the peak systolic ejection rate (PER,ml/s). A new index was proposed as the PER normalized for LVEDV and LVM (PER/V*M, 1/s*g) and compared in the examined groups.
Results: Mean LVEF was slightly lower in CAD and CABG (63±10%) than in controls (68±5%), but LVEDV were comparable (147±37 vs 135±29ml), and LVM significantly higher (158±42 vs 122±25.g), as expected. In patients with ischemic HF all traditional parameters were most abnormal (32±12%, 263±70ml and 205±50g, resp.). The PER reached 412±98 in controls, 384±102 in CAD, 382±98 in CABG and 325±113 in HF (p<0.001 ANOVA). The PER/V*M differed most significantly between controls and CAD (2.6±0.6 vs 1.9±0.7), CABG (1.8±0.7) and HF (0.7±0.3; p<0.001 ANOVA). The abnormal value of PER/V*M (established in controls log10<0.43) was observed in 58 out of 185 CAD-pts (31%) and 41 out of 101 CABG-pts (40%), and in all HF patients, while low LVEF (<50%) was observed in 15 (8%), 11 (11%) and 25 (96%) patients, resp.
Conclusions: Cardiac CT allows for determination of volume-ejection rate based parameters of LV contractility. Abnormal PER/V*M suggested the presence of contractile dysfunction in approximately 1/3 chronic CAD and post-CABG patients, in whom LVEF was mostly preserved. Detection of contractile abnormalities might supplement LVEF as a measure of systolic dysfunction.

TREATING VENTRICULAR DYSFUNCTION

P5579 | BEDSIDE
Effects of low dose dopamine infusion on ventriculoarterial coupling, ventricular efficiency and renal function in patients with acute decompensated systolic heart failure

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Our purpose was to assess the effects of the combination of low dose dopamine and furosemide on optimising ventriculoarterial coupling (VAC), ventricular efficiency and their potential correlation with renal function as compared with those of high or low dose furosemide alone in patients with acutely decompensated systolic heart failure (ADHF). A subgroup of 42 patients of the Dopamine in Acute Decompensated Heart Failure II study were echocardiographically assessed regarding their VAC and ventricular efficiency status at 0 and 24 hours post protocol initiation. Each patient was randomised to one of the following groups: high dose furosemide (20mg/hr), low-dose dopamine (5μgr/kg/min) with low dose furosemide (5mg/hr) and low dose furosemide alone (5mg/hr). Protocol duration was 8 hours and all patients received standardised treatment until further assessment (40mg furosemide iv q12 hours). Renal function was assessed by means of serum creatinine and creatinine clearance at 0 and 24 hours. Patient groups did not differ significantly regarding their baseline status, VAC and ventricular efficiency. Analysis showed that VAC was significantly improved (shift towards 1) in the combination group (p=0.032) and a similar trend was noted regarding ventricular efficiency (p=0.10, favouring dopamine-furosemide group). Significant correlation was noted between VAC improvement and efficiency optimisation (coefficient 0,974, p<0,001). Renal function improved significantly in the combination group when assessed by serum creatinine trends (p=0.026) while clearance trend was again suggestive of improvement (p=0.076). Interestingly, a strong positive correlation was noted between serum creatinine improvement and VAC - ventricular efficiency across groups (coefficient 0.234, p=0.04 and coefficient 0.250, p=0.028 respectively). No differences were noted regarding diuresis, urea trends, neutrophil to lymphocyte ratio, BNP within the first 24hrs and hospitalisation duration.
Conclusion: The combination of low dose dopamine and low dose furosemide seems to improve VAC in patients with ADHF, thus increasing stroke work and improving peripheral perfusion, negating the acute unfavourable haemodynamic effects of furosemide infusion. Renal function, a sensitive indicator of perfusion, improved significantly more in the dopamine group; while no deterioration in myocardial energy efficiency was observed, a side-effect of inotropes (trend was to the opposite direction), suggesting that improved VAC per se and not increased contractility drove our findings. Therefore, dopamine may be a useful adjunctive treatment in ADHF patients.

P5580 | BEDSIDE

Intra-aortic balloon pump effects on macrocirculation and tissue microcirculation in cardiogenic shock patients supported by venoarterial extracorporeal membrane oxygenation

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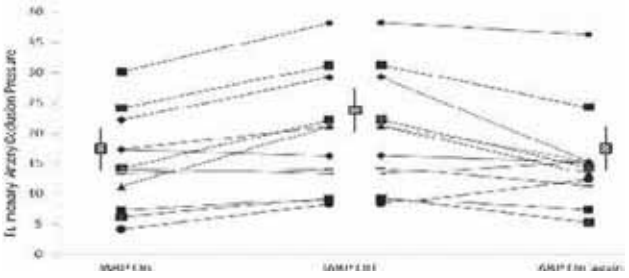
Aims: This study was designed to assess the effects on macrocirculation and tissue microcirculation of adding an intra-aortic balloon pump (IABP) to peripheral venoarterial–extracorporeal membrane oxygenation (VA-ECMO) in patients with severe cardiogenic shock and little/ no residual left ventricular (LV) ejection.
Methods and results: Clinical, Doppler echocardiography and pulmonary artery-derived hemodynamic parameters, and cerebral and thenar eminence tissue oxygenation (StO2) and side-stream dark-field (SDF) imaging of sublingual microcirculation were evaluated in 12 consecutive patients before, and 30 minutes after interrupting and restarting IABP. Stopping IABP was associated with higher pulmonary artery-occlusion pressure (PAOP) (19±10 vs. 15±8 mmHg, P=0.01), increased LV end-systolic (51±13 vs. 50±14 mm, P=0.05) and end-diastolic (55±13 vs. 52±14 mm, P=0.003) dimensions and decreased pulse pressure (15±13 vs 29±22 mmHg, P=0.02). Maximum PAOP reduction when the IAPB was restarted was observed in the 7 patients whose PAOP was >15 mmHg when IABP was off (–6.6±4.3 vs. –0.6±3.4 mmHg, respectively). Thenar eminence and brain StO2 and SDF-assessed sublingual microcirculation were unchanged by stopping and restarting IABP.



Conclusion: Restoring pulsatility and decreasing LV afterload with IABP was associated with smaller LV dimensions and lower pulmonary artery pressures, but did not affect microcirculation parameters in cardiogenic shock patients with little/no residual LV ejection while on peripheral VA-ECMO. IABP might prevent severe hydrostatic pulmonary edema in this context.

P5581 | BEDSIDE

A phase II randomized, double-blind, placebo controlled study to evaluate the safety and efficacy of an endomyocardial injection of hSDF-1 plasmid to ischemic heart failure patients, the STOP-HF trial

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Purpose: Stromal cell-derived factor-1 (SDF-1) promotes tissue repair by increasing cell survival, endogenous stem cell recruitment and vasculogenesis. In an open-label Phase I study, endomyocardial injection of a non -viral DNA plasmid encoding human SDF-1 in ischemic heart failure (IHF) patients led to improved clinical status. The purpose of STOP-HF, a Phase II multi-center double blind randomized placebo-controlled trial, is to study the effects of a single-dose of SDF-1 plasmid delivered via endomyocardial injection on clinical parameters and outcomes.
Methods: 93 IHF subjects on stable medical therapy with reduced LV function (EF ≤40%), poor Minnesota Living with Heart Failure Questionnaire scores (MLWHFQ >20 points) and limited six minute walk distances (6MWd ≤400 meters) were randomized 1:1:1 to receive 15 or 30 mg of SDF-1 plasmid or placebo via 15 injections through the BioCardia Helical Infusion Catheter. The primary efficacy endpoint is a composite change in MLWHFQ and 6MWd at 4 months. Additional efficacy assessments included NYHA class, biomarkers, echocardiographic parameters and exercise capacity.
Results: Enrollment was completed in October of 2013. Profile of subjects at baseline (mean ± SD): age 65±9 years, LVEF 29±7%, MLWHFQ 50±20 points and 6MWd 289±99 meters. All subjects received injections with 96% of patients receiving all 15 injections. To date, 761 follow up months have been completed, all subjects beyond 1-month are free of unanticipated serious adverse events related to study drug. Four-month efficacy results will be available in April 2014.
Conclusions: STOP-HF was designed to test the hypothesis that up-regulating endogenous stem cell trafficking to the heart improves clinical status and outcomes in patients with symptomatic chronic heart failure. To date, the results of STOP-HF continue to demonstrate the strong safety profile of SDF-1 plasmid delivery. Primary efficacy endpoint data will be presented.

P5582 | BEDSIDE

Application of novel hemodynamic subsets in predicting the need for inotropic support in congestive heart failure

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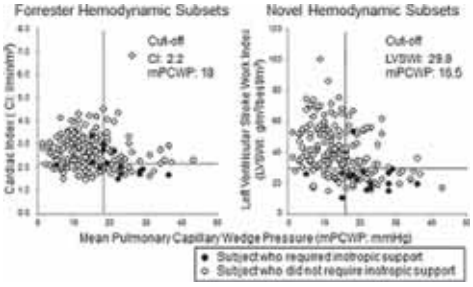
Purpose: We aimed to elucidate the best hemodynamic parameter to propose novel hemodynamic subsets in predicting the need for inotropic support in patients with congestive heart failure (CHF).
Methods: We performed right heart catheterization (RHC) in 197 consecutive HF patients (67±15 years old, 129 males) on hospital admission. Left ventricular stroke work index (LVSWI) was estimated by the formula: (mean blood pressure – mean pulmonary capillary wedge pressure (PCWP)) * stroke volume index * 0.0136 (g/m^2/beat/m^2).
Results: Sixteen (8.1%) patients required inotropic support during hospitalization. Among hemodynamic variables including cardiac index, stroke volume index, mean PCWP, and left and right ventricular stroke work index, LVSWI was identified as the best predictor of inotropic need with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.85 (95% CI; 0.76-0.95, P<0.01), and the best cutoff value was 29.8 g/m^2/beat with sensitivity of 94% and specificity of 75%. In contrast, the AUC of cardiac index was only 0.73 (95% CI; 0.60-0.86, P<0.01). The combination of LVSWI and mean PCWP had greater ability for predicting the need for inotropic support compared with the use of the Forrester hemodynamic subsets (Figure).



Forrester and novel hemodynamic subsets.

Conclusions: The novel hemodynamic subsets based on combined RHC-derived LVSWI and mean PCWP has great utility in predicting the need for inotropic support and can guide an individualized therapeutic strategy in CHF.

P5583 | BENCH

High-fat diet ameliorates left ventricular remodelling and dysfunction

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Aims: Interleukin 13 receptor α1 (IL-13 Rα1) deficiency leads to the development of dilated cardiomyopathy (DCM) and left ventricular (LV) dysfunction in mice. We aimed to determine the role of a high-fat diet on LV remodelling and dysfunction in IL-13 Rα1-deficient mice.
Methods and results: We compared the outcome of 6-week old Il13ra1–/– (prone to DCM) with wild-type normal mice placed on an 18-week high-fat diet. Il13ra1–/– mice gained more weight than controls during the study period. Body composition was analyzed in-vivo using nuclear magnetic resonance. Fat-to-lean mass ratio was higher in Il13ra1–/– mice compared with controls (0.79±0.03 and 0.63±0.02, respectively, p<0.01). An echocardiography study was performed at the age of 24 weeks to evaluate the possible effect on cardiac dysfunction in previously characterized Il13ra1–/– mice. Surprisingly, the high-fat diet normalized and prevented the development of DCM in the Il13ra1–/– mice. Cardiac indices such as LV ejection fraction (53.66±6.7 vs. 50.29±4.23%, p=0.66) posterior wall diastolic thickness (0.81±0.03 vs. 0.83±0.02 mm) and LV diastolic dimension

(4.00±0.12 vs. 3.8±0.09 mm, p=0.21; n=6-9 per group), were similar in the DCM and normal mice, respectively, after 18 weeks of the high fat diet.
Conclusion: A high-fat diet prevents the development of adverse cardiac remodelling and dysfunction in mice prone to cardiomyopathy. Clinical studies are needed to confirm our provocative findings and determine the optimal diet composition in vulnerable patients with cardiomyopathy and heart failure.

P5584 | BEDSIDE
Impact of infiltrated immune-mediated cells in myocardium on long-term prognosis in patients with dilated cardiomyopathy

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Background: The causes of dilated cardiomyopathy (DCM) have yet undetermined, but there is growing evidence that persistent inflammation in myocardium plays some pathophysiological role in DCM. Macrophages, along with dendritic cells (DCs), are characterized as antigen-presenting cells to the immune system and vitally important to regulate its consequential inflammatory response. A recent study showed macrophages and DCs are found in endomyocardial biopsy specimens from patients with DCM. However, the relationship between infiltration of immune-mediated cells and the prognosis of DCM has not well understood.
Method: A total of 110 consecutive patients with heart failure, who underwent right ventricular endomyocardial biopsy as diagnostic procedure in 2005 at our institution were reviewed. Of them, by excluding ischemic cardiomyopathy, hypertrophic cardiomyopathy, myocarditis, and secondary cardiomyopathy such as sarcoidosis and amyloidosis, 39 patients who were consequently diagnosed as DCM were enrolled in the study. We stained stored biopsy samples with antibodies specific for CD3 (T lymphocytes), CD68 (macrophages), CD163 (M2 macrophages), and CD209 (DCs) to count the infiltrated cells. We also obtained each patients' clinical data in medical records from diagnosis for up to 8 years.
Results: During the observation period, 6 patients (15%) died (1.8-7.7 years from diagnosis, Group D). Those patients showed no different baseline characteristics at diagnosis, including sex, age, LV ejection fraction, LV end-diastolic dimension, serum Na, creatinine, total protein, total bilirubin and plasma BNP levels, from those who survived (Group S). The number of infiltrated CD68 and CD163 was greater in Group D compared to Group S (31±5 vs. 17±2/mm^2, p=0.01, and 15±3 vs. 8±1 /mm^2, p=0.05). On the other hand, infiltrated CD3 did not differ between the groups (16±4 vs. 9±2 /mm^2, p=NS).The number of CD209 are positively correlated with those of CD68 (R=0.42, p=0.009) and CD163 (R=0.64, p<0.0001).
Conclusions: Despite similar clinical background, patients with worse long-term prognosis showed more infiltrated macrophages in endomyocardial biopsy specimens at diagnosis of DCM. In addition, infiltration of DCs was associated with that of macrophages into myocardium, suggesting the possible role of immune-mediated cells in the pathophysiology of DCM.

P5585 | BEDSIDE
Models for management of acute heart failure: a comparison of acute heart failure pathways at two UK Tertiary Centres

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Background: HF due to reduced ejection fraction (EF) is a complex syndrome with prognostic, evidence based therapy. In order to best manage the disease and improve short and long term outcomes, identification of patients is key.
Two linked, tertiary centre hospitals with established Heart Failure (HF) teams comprising consultants, dedicated specialist registrars and specialist nurses, developed different pathways for identification and referral of such patients. This abstract presents a comparison of their activity using these pathways to previous models of working.
Methods: At site 1, an NT-proBNP pathway was developed such that anyone with signs and symptoms of HF with an NT-proBNP >2000ng/L or BNP >400ng/L was referred. At site 2 those admitted with signs and symptoms of HF underwent a transthoracic echocardiogram (TTE) prior to referral. Data on both sites was collected over a 4 month period and comparison is made with 4 months of the previous year when neither pathway was in use.
Results: Site 1 saw 212 patients of whom 97 (46%) were male; mean age 75 yrs. Median time to review was 1 day from referral (0-1) but 4 days from admission (2-9). 33% had reduced EF. Median length of stay (LOS) did not change (15 days) however 30-day readmission rate was significantly decreased using the new pathway (20% vs 13%; p=0.03)
Site 2 reviewed 228 patients of whom 124 (54%) were male; mean age 70 yrs. Median time to review was 1 day from referral (0-1) and 4 days from admission (1-7). 87% had reduced EF. Median LOS did not change (14 vs 12 days; p=0.23). 30-day readmission rate was reduced but not significantly different (7.6% vs 1.0%; p=0.13)
Conclusion: This study shows that both an NT-proBNP/BNP and echo driven pathway for identification and referral of patients with acute decompensated HF is feasible. Site 2's TTE driven pathway is associated with an increased specificity for those with HF and reduced EF.
Both pathways lead to reduced readmission rates at 1 month; however there is no significant difference in LOS.

P5586 | BEDSIDE
How accurate is clinical assessment in the estimation of central venous pressure in acute heart failure? Insights from a prospective study

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Background: Clinical assessment of signs of volume overload including elevated neck veins is important in the early diagnosis of acute heart failure (AHF). However, it is largely unknown how accurate is routine clinical assessment in the estimation of central venous pressure (CVP) in patients with AHF.
Methods: In 216 unselected AHF patients presenting to the Emergency Department (ED) neck veins were examined by the treating ED physician in an observational prospective study. CVP was measured using peripheral venous compression sonography at the forearm, a novel non-invasive method shown to be close correlated with invasive measurements, in a blinded fashion. The measures were done before the administration of vasodilators or diuretics. CVP determinations were registered as continuous data, and CVP >12mmHg was considered as elevated.
Results: In the study cohort [58% men, median age 80 years, left ventricular ejection fraction 40%, B-type natriuretic peptide 1372 pg/mL body mass index 26,4, neck veins were rated as normal in 32,4%, a positive hepatojugular reflex (neck veins normal at rest but distended during increased reflux) in 11,6% and distended already at rest in 56% of AHF patients. Interestingly, the median CVP values were 8,5mmHg (IQR: 5,2-12,6mmHg), 8,1mmHg (IQR: 5,5-14,4mmHg), and 9,6mmHg (IQR: 5,5-12,6mmHg), respectively. A Kruskal-Wallis test showed no significant difference (p=0,72). Physical examination had a sensitivity of 54% to detect an elevated CVP defined as CVP>12mmHg. Findings were similar in predefined subgroups including the obese, the elderly, and women.
Conclusion: Clinical estimation of CVP by physical examination of the neck veins in AHF is highly inaccurate. Reasons may include poor training of ED physicians in the pitfalls of examining neck veins (e.g. the critical distinction between normal and not assessable neck veins) and cheating/extrapolation (AHF has been diagnosed independent of this variable and findings are rated to match the presumed diagnosis.

P5587 | BEDSIDE
A heart-failure led one-stop diagnostic service for breathlessness: initial experiences and diagnostic yield

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Purpose: Breathlessness is the most common presenting complaint in heart failure, a condition known to be under-diagnosed. Primary care physicians are calling for direct access symptom-based diagnostic services to optimise secondary care referral pathways. We established a breathlessness clinic staffed by members of a tertiary centre heart failure team, and assessed its potential clinical utility for detecting heart failure (and other cardiorespiratory disorders) that require further investigation and/or treatment.
Methods: Primary care physicians were invited to refer patients for one-stop testing, including ECG, B-natriuretic peptide (BNP), spirometry, echocardiography, cardiopulmonary exercise testing (CPX) and clinical assessment.
Results: 191 patients were assessed over 2.6 years (90 male, median age 75 years). Median body mass index was 29.1 kg/m^2; 80 patients met criteria for obesity. Breathlessness was the presenting symptom in 82%, oedema in 12% and cough in 4%. 64 patients were known to have pre-existing cardiac conditions (including 13 with heart failure) and 56 had pre-existing respiratory conditions.
Left ventricular systolic function was mildly, moderately and severely impaired in 7%, 2% and 3% of patients respectively, with impaired diastolic function in a further 17% and valvular disease of at least moderate severity in 10%. Natriuretic peptides were elevated (BNP≥100 or NT-proBNP≥400) in 30% of the subjects in whom samples were taken. 58% of 120 patients undergoing CPX had reduced exercise capacity (defined by a peak VO2<85% predicted).
A cause for the patient's breathlessness was found in 80% with a new cardiac diagnosis made in 17% (HFrEF 4%, HFpEF 6%, likely angina 3%, arrhythmia 2%, valvular disease 2%) and new respiratory diagnosis in 10%. 38% of subjects were reassured with no requirement for further secondary-level investigations or review.
Conclusions: Although breathlessness is the most common presenting symptom in heart failure, only a small proportion of subjects with unselected referral to a community breathlessness service had heart failure with a reduced ejection fraction requiring further expert investigation and management. This one-stop approach in breathless patients offers a streamlined assessment with the additional potential for fully reassuring patients of the absence of significant cardiac or respiratory pathology.

P5588 | BENCH

Diagnosis and therapy monitoring of idiopathic giant cell myocarditis and cardiac sarcoidosis by myocardial gene expression profiling

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Objective: Improvement of clinical diagnostics of idiopathic giant cell myocarditis (IGCM) and cardiac sarcoidosis (CS), two frequently fatal human myocardial diseases. Currently, IGCM and CS are diagnosed based on differential patterns of inflammatory cell infiltration and non-caseating granulomas in histological sections of endomyocardial biopsies (EMB), after heart explantation or postmortem. We report on a method for improved differential diagnosis by myocardial gene expression profiling in EMBs.
Methods: We examined gene expression profiles in EMBs from 10 patients with histopathologically proven IGCM, 10 with CS, 18 with active myocarditis (MCA), and 80 inflammation-free control subjects by quantitative RT-QPCR. We identified distinct differential profiles that allowed a clear discrimination of tissues harboring giant cells (IGCS, CS) from those with MCA or inflammation-free controls.
Results: The expression levels of genes coding for cytokines or chemokines (CCL20, IFNB1, IL6, IL17D; $p<0.05$), cellular receptors (ADIPOR2, CCR5, CCR6, TLR4, TLR8; $p<0.05$) and proteins involved in the mitochondrial energy metabolism (CPT1, CYB, DHODH; $p<0.05$) were deregulated in 2 to 300fold range, respectively. Bioinformatic analyses and correlation of the gene expression data with immunohistochemical findings provided novel information regarding the differential cellular and molecular pathomechanisms in IGCM, CS and MCA.
Conclusion: Myocardial gene expression profiling is a reliable method to predict the presence of multinuclear giant cells in the myocardium, even without a direct histological proof in single small EMB sections, and thus to reduce the risk of sampling errors. This profiling also facilitates the discrimination between IGCM and CS, as two different clinical entities that require immediate and tailored differential therapy.

P5589 | BEDSIDE

Endovascular versus epicardial lead placement for resynchronization therapy?

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Objective: To study the clinical outcome in Cardiac Resyncrhonization Therapy (CRT)-eligible patients of transvenous versus epicardial left ventricular (LV) lead implantation.
Methods: A total of 290 consecutive CRT recipients from an ongoing, single center registry were included in the present analysis. The follow-up was 7,76±2,33 years. Patients were selected for CRT according to the presence of LV ejection fraction (LVEF) ≤35%, heart failure (HF) symptons despite optimal medical therapy, and a QRS duration ≥120ms. The LV lead placement was guided by an intraoperative coronary sinus (CS) occlusive venogram. LV leads were placed in the lateral (54,1%,n=157), posterolateral (19%, n=55), anterolateral (15,9%, n=46), interventricular anterior (1,7%, n=5) coronary veins and epicardial placement (9,3%, n=27).
Results: Both groups demonstrated improvement in the ejection fraction (EF) at 6 months. The baseline EF, LVESD, LVEDD was similar for the transvenous and epicardial groups, with no difference in the change over 6 months (Table 1). The baseline NYHA class was a median of III and improved to II in boths groups at 6 months. A total of 93 deaths: 19 (38,8%) HF in lateral vein, 10 (58,8%) HF in anterolateral vein, 10 (50%) HF in posterolateral vein, 3 (7%) HF in interauricular vein and 1 (50%) HF in epicardial LV. The second cause was infectious (11,8%, n=11) and the third cause tumors (10,8%, n=10). In the transvenous group 102p (40,2%) needed new hospitalizations, in the epicardic group 6 (23,1%), p=0,089. The overall survival was worse in epicardic group versus endovascular group (χ^2=9,490; df=1; p=0.002).

LV position– echocardiographic parameter

	3	Baseline		Six months later		
	Epicardial LV lead n=27	Endovascular LV lead n=263	p	Epicardial LV lead n=27	Endovascular LV lead n=263	p
EF	35,20±10,96	34,54±16,04	0,930	42,53±11,26	37,48±12,19	0,099
LVESD	47,40±13,27	53,38±12,53	0,328	48,24±10,23	50,86±12,18	0,387
LVEDD	58,80±9,88	83,17±13,6	0,606	58,80±9,88	83,18±13,6	0,298
LA	36,8±21,37	47,62±11,19	0,091	36,8±21,37	47,61±11,59	0,196

EF: ejection fraction; LVESD: left ventricular end systolic diameter; LVEDD: left ventricular end diastolic diameter.

Conclusions: There was no demonstrable superiority of outcomes for the patients treated with surgically placed leads versus conventional transvenous lead placement. The overall survival in epicardial group was worse than transvenous group probably there were less patients than in transvenous group.

P5590 | BENCH

Modification of cardiac disease by histone deacetylase 6 in pressure-overloaded hypertrophy

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Background: Alpha-tubulin, a component of microtubules, is acetylated at the amino acid lysine at position 14, and its deacetylation is regulated by histone deacetylase 6 (HDAC6). Although this acetylation of tubulin may be associated with intracellular the transport system and cellular function in the cardiomyocytes, the functional role of acetylated tubulin in disease conditions such as a pressure-overloaded hypertrophy and disease progression to heart failure remains uncertain.
Methods and results: Modification of cardiac HDAC6 was performed by transgenic (TG) overexpression of the active HDAC6 and dominant negative HDAC6 (H216A, H611A) proteins specifically in the cardiomyocytes. Overexpression of active HDAC6 significantly reduced acetylated tubulin levels and overexpression of dominant negative HDAC6 significantly increased it in the mouse heart, suggesting that HDAC6 can regulate cardiac tubulin deacetylation. Neither histological alteration nor alteration of cardiac function determined by echocardiography was seen in the active and dominant negative TG mouse hearts from mice one year of age or older. These results suggest that HDAC6 activity has no critical role in mouse cardiomyocytes. To analyze the role of HDAC6 and acetylated tubulin in disease conditions, we studied the pressure overloaded stress responses in TG mice hearts. Pressure-overloaded hypertrophy was generated by surgical thoracic aortic banding (TAC). Cardiac hypertrophy was observed in nontransgenic (NTG) TAC mouse hearts without reduction in shortening fraction by echocardiography two weeks after surgery. Cardiac acetylated tubulin was decreased in the hypertrophic NTG mouse hearts compared with that in the NTG mouse hearts. A marked reduction in the shortening fraction and dilated chamber dilatation was detected in the active HDAC6 TG mouse hearts two weeks after surgery. Sustained low level of acetylated tubulin was observed in the TAC HDAC6 active TG mouse hearts, suggesting that activation of HADC6 with concomitant reduction in acetylated tubulin can worsen cardiac disease in pressure-overloaded hypertrophy.
Conclusion: Cardiac HDAC6 activity and the cardiac acetylated tubulin level may be critical factors involved in cardiac disease in pressure-overloaded hypertrophy.

HEART FAILURE, PATHOPHYSIOLOGY AND PROGNOSIS

P5592 | SPOTLIGHT

Parameters predicting the preserved ICD indication for primary prevention after optimal medical treatment in patients with chronic systolic heart failure

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Background: Optimization of medical treatment (OMT) before initiation of device therapy (DT) is recommended by guidelines (Class I) for chronic systolic heart failure (HFrEF) patients (pts). Until present, however, we have limited information about the extent to which OMT can reduce the proportion of pts with ICD indication for primary prevention (PP), and about parameters which are able to predict a preserved indication of PP ICD.
Aim: The aim of our study was to investigate the proportion of pts who fulfilled the indication criteria of PP ICD before and after OMT and to assess the potential prognostic factors that may predict the therapeutic answer.
Methods: Parameters of 693 pts managed at our Heart Failure Clinic (mean age: 62.5±24.0 years, ischemic etiology: 49.1%, NYHA class: 2.95±0.94, left ventricular ejection fraction: 30.9±9.3%) were evaluated. We assessed clinical and echocardiographic parameters of the pts before OMT and 6 months later (after drug-titration and 3 months use of OMT). Prognostic value of several clinical, echocardiographic, ECG and laboratory parameters was investigated by logistic regression analysis.
Results: From 693 pts with HFrEF 253 (36.5%) met the indication criteria of PP ICD at the first examination, before OMT. During the 6 months follow up 4 of 253 pts died. From the remaining 249 pts 157 (63%) improved on OMT in respect of LVEF (53%), NYHA class (32%) or both (22%) to an extent that ICD was not indicated any longer. After OMT, PP ICD was indicated only in 13.4% of all HFrEF pts. Univariate analysis proved the predictive value of baseline ejection fraction (EF≤25.5% vs EF>25.5%; OR: 2.97; $p<0.001$), end-diastolic diameter (EDD>70mm vs EDD≤70mm; OR: 3.41; $p<0.001$), end-systolic diameter (ESD>59mm vs ESD≤59mm; OR: 3.17; $p<0.001$), systolic blood pressure (Psyst≤130mmHg vs Psyst>130mmHg; OR: 2.66; $p<0.01$), and the presence of left bundle branch block (OR: 1.99; $p<0.05$). Multivariate logistic regression analysis demonstrated that baseline ejection fraction (EF≤25.5% vs EF>25.5%; OR: 2.40; $p<0.01$), end-diastolic diameter (EDD>70mm vs EDD≤70mm; OR: 2.75; $p<0.05$) and systolic blood pressure (Psyst≤130mmHg vs Psyst>130mmHg; OR: 2.376; $p<0.05$) could predict the preservance of PP ICD indication on OMT.
Conclusions: In pts with HFrEF applying OMT before decision on PP ICD implantation can significantly decrease the number of pts fulfilling the criteria of PP

ICD indication. Significantly impaired left ventricular ejection fraction, left ventricular dilatation and low systolic blood pressure could predict the preservance of PP ICD indication on OMT.

P5593 | BEDSIDE
Liver stiffness measured by transient elastography predicts clinical events in patients with heart failure

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Background: Passive liver congestion due to elevated right-sided filling pressure is a common finding in patients with heart failure (HF). However, the clinical impact of liver congestion on HF outcomes has been poorly described. Transient elastography is a new non-invasive method to evaluate liver stiffness (LS). We investigated the impact of LS on clinical outcomes in HF patients.
Methods: LS values in 157 consecutive HF patients (age 64±15 years, male 69%, LVEF 44±18%) were determined before discharge using a (...) device. Patients with invalid liver stiffness measurements due to severe obesity, narrow intercostal space and substantial ascites were excluded. Patients were followed for cardiac death or rehospitalization due to HF. ROC curve analysis was used to derive optimal cutoff value for predicting outcomes. Cox proportional-hazards regression was used to adjust for the effect of differences in pertinent covariates on the clinical event rate.
Results: The median of LS in our study patients was 6.5 kPa (range 2.3 - 39.7). Twenty patients (13%) died or were hospitalized for decompensated HF after a mean follow-up of 75±28 days. ROC curve analysis of LS for predicting events revealed an optimal cutoff value of 10.1 kPa. The cardiac event rate was higher in patients with high LS (≥10.1 kPa) than in those with low LS (<10.1 kPa) (37% vs. 4%, p<0.0001). In univariate analysis, LS was related to higher risk of clinical events (crude HR: 1.11, 95% CI: 1.07 - 1.15, p<0.0001). Even after adjusting for age, sex, total bilirubin, LVEF, and BNP, LS was still associated with a higher event rate (adjusted HR: 1.10, 95% CI: 1.05 - 1.15, p=0.0001).

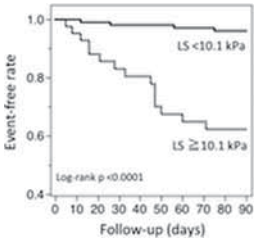

Figure 1

Conclusions: LS offers a rapid and noninvasive diagnostic method to identify patients at a risk of cardiac death or rehospitalization for HF.

P5594 | BEDSIDE
Antigen carbohydrate 125 predicts 30-day readmission in acute heart failure

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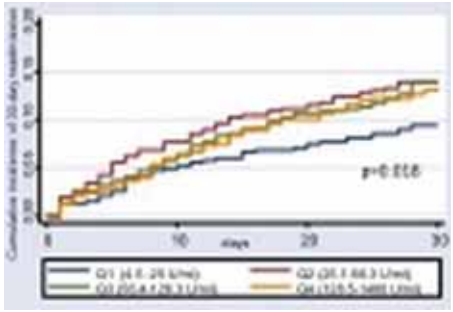
Background: Early readmission after a hospitalization for acute heart failure (AHF) remains prohibitively high and there are not well stablished markers for risk stratification. Plasma antigen carbohydrate 125 (CA125) has emerged as a biomarker related to fluid overload severity of the disease and adverse outcomes. We aimed to evaluate the performance of CA125 to predict 30-day readmission risk in an unelected cohort of patients admitted for AHF.
Methods: We included 1869 consecutive patients discharged alive with AHF diagnosis in a third level hospital (2004-2013). CA125 was measured before discharge and categorized in quartiles (Q). Cox regression analysis adapted for competing events (death) was used to evaluate the independent association between CA125 and the risk of unplanned 30-day readmission. More than 40 variables were evaluated in the multivariate analysis.
Results: At 30 days after discharge, 11 (0.6%) and 236 (12.6%) patients died and were readmitted, respectively. Cumulative incidence for readmission was lower for Q1 (CA125 ≤25U/ml) compared to those patients in the upper quartiles (figure below). In the multivariate analysis, patients in the lower quartiles of CA125 exhibited a 30% of risk reduction compared to those in the upper quartiles (HR: 0.70, CI 95%=0.51-0.99, p=0.046). Natriuretic peptides did not predict the risk of readmission.
Conclusion: Low CA125 identified a subset of patients with lower risk of unplanned 30-day readmission after an episode of AHF.


CA125 and 30-day readmission for AHF.

P5595 | BENCH
Archaeosomal microparticles ridding metalloproteases from the serum may explain protection against heart failure in chagasic patients with asymptomatic indeterminate form

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Background: Microparticles (MPs) in the serum have been related with presence of Heart Failure (HF). HF occurs in 30% of Trypanosoma cruzi infected chagasic individuals, being a useful model to study of MPs. In previous work we found in chagasic endomyocardial biopsies that archaeal gene encoded electron dense lipidic (ED) organelles are possibly archaeosomes that entrap extracellular proteins having the function of ridding abnormal proteins, and are increased in asymptomatic indeterminate form (IF) patients. Electron lucent pathogenic archaea were increased in HF patients, possibly releasing metalloprotease.
Objective: In this work we searched if ED MPs (archaeosomes) are increased in the serum of IF, entrapping Archaemetzincin-1 (AMZ1), a metalloprotease widely seen in archaea, compared with serum of HF patients.
Material and methods: Sera from 8 HF and 7 from IF chagasic patients were submitted to a technique of MP separation, in a mannitol/ sucrose rich solution. After centrifugation, MPs in the pellet and in the supernatant were studied at immunoeletron microscopy, using anti-AMZ1 monoclonal antibody (Novus Biologicals). The mean number/ μm^2 of ED MPs <100nm and of AMZ1 positive dots intra or extra ED MPs were obtained from 10 photos/case in 50K magnification.
Results: In the supernatant, ED MPs were present in higher numbers in IF (33.4±50.9) than in HF (0.2±1.1), P<0.001; in IF the ED MPs contained AMZ1 positive dots (1.6±3.7), in positive correlation with numbers of ED MPs (r=0.47, P<0.0001) and in HF, ED MPs were almost absent and did not contain AMZ1 dots.
In the pellet, the amount of ED MPs did not differ between HF versus IF groups (3.6±5.9 vs 2.5±4.9, P=0.74), but AMZ1 positive dots extra ED MPs were significantly increased in HF (80.5±132.3) compared to IF (15.5±19.27), P<0.001. The numbers of ED MPs correlated negatively with AMZ1 extra ED MPs in HF (r= -0.63, P<0.001), but not in IF (r=0.13, P=0.34).
Conclusion: ED MPs <100nm in the serum of IF chagasic patients seem to be archaeosomes, which remove free metalloprotease particles, preventing development of HF whereas the absence of the ED MPs is associated with increase of free metalloprotease in serum of HF patients. This is a first human documentation of removal of free abnormal protein from the serum by archaeosomes.

P5596 | BEDSIDE
Myocardial strain but not ejection fraction adds incremental value to clinical predictors of readmission for heart failure

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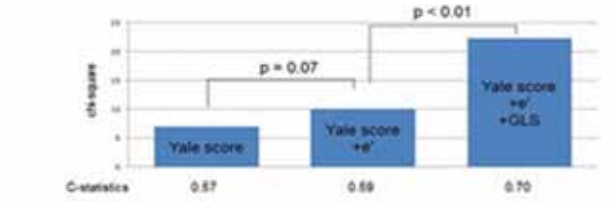
Background: Risk stratification for heart failure (HF) readmission might enable targeting resources to prevent readmission in the higher risk pts. Unfortunately, clinical risk scores have limited predictive value, and the contribution of EF is variable, based on prevalence of HF and preserved EF. Strain has been shown to improve prognostic assessment over traditional parameters. We hypothesized that adjustment of risk score with strain would enable a more accurate appreciation of risk.
Methods: 468 pts who underwent echo at the time of the first admission for HF were followed for 30-day hospital readmission or death. Three validated risk scores were calculated (#1: Philbin 1999, #2: Krumholtz 2000, #3 (including EF, Yale score): Keenan 2008). Echo variables were binalized using the external criteria. Assignment of each echo parameter to clinical score was decided according to β coefficient in Cox multivariate analysis. Strain was measured using speckle tracking. We used nested Cox models and net reclassification improvement (NRI) to assess the incremental benefit.
Results: Outcome was reported in 92 pts. Only the Yale score was associated with outcome. Global longitudinal strain (GLS: cutoff -12%), global circumferential strain (cutoff -10.7%), and e' (cutoff 5cm/s) were associated with outcome after adjusted by Yale score (all p<0.10). In sequential Cox models, although the Yale score model was not improved by adding e', the model based on Yale score and e' was significantly improved by adding GLS (Figure) Adding e' or GLS to Yale

score led to a significant reclassification improvement (Yale+e': NRI=0.23, p=0.05, Yale+GLS: NRI=0.45, p<0.01).



Variable	Model 1 (Yale) Chi-square=7.0 HR (95%CI), p Value	Model 2 (Yale+e') Chi-square=10.2 HR (95%CI), p Value	Model 3 (Yale+e'+GLS) Chi-square=22.4 HR (95%CI), p Value
Yale score	1.07 (1.02-1.13), p=0.01	1.07 (1.02-1.13), p=0.01	1.06 (1.01-1.12), p=0.03
e'		1.46 (0.97-2.20), p=0.07	1.31 (0.87-1.98), p=0.20
GLS			2.53 (1.51-4.26), p<0.01

Conclusion: Imaging parameters provide incremental value over the validated risk score for predicting 30-day readmission in pts with HF.

P5597 | BEDSIDE

Relationship between LV contractility and coronary flow reserve in non-ischemic dilated cardiomyopathy: a noninvasive stress-echo study

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Background: LV contractility plays an important diagnostic and prognostic role in non-ischemic dilated cardiomyopathy (IDC). Systolic pressure/end-systolic volume relationship (SP/ESVi) is a useful method for evaluating LV myocardial contractility during stress echocardiography (SE). Coronary flow reserve (CFR) on left anterior descending (LAD) can be reduced in IDC.
Aim: To assess the relationship between SP/ESVi and CFR on LAD in IDC patients.
Methods: We enrolled 134 IDC patients (98 men; 62±12 years, mean value of ejection fraction: 34±8%) and 38 age-sex matched normal subjects as control's group (29 men; 65±11 years, mean value of ejection fraction: 61±4%). All underwent dipyridamole SE (dip-SE 0.84 mg/kg in 6'). CFR was defined as the ratio between maximal vasodilation and rest peak diastolic flow velocity in LAD. SP/ESVI was defined as systolic cuff pressure/end-systolic volume index difference between rest-peak dip-SE.
Results: SP/ESVi was 0.25±0.74 mmHg/ml/m^2 in IDC patients and 3.90±2.67 mmHg/ml/m^2 in controls. SP/ESVi was not related to ejection fraction at rest, while it was directly related to ejection fraction at peak dip-SE (r=0.448, p<0.001) and rest-stress difference in ejection fraction (r=0.435, p<0.001). CFR on LAD was abnormal (<2) in 66 (49%) IDC patients. SP/ESVi was directly related to CFR on LAD (r=0.369, p=0.001, Figure, red points) in IDC patients: LV contractile reserve affected increase in CFR, while in controls we did not find relationship between SP/ESVi and CFR (Fig. 1, green points).

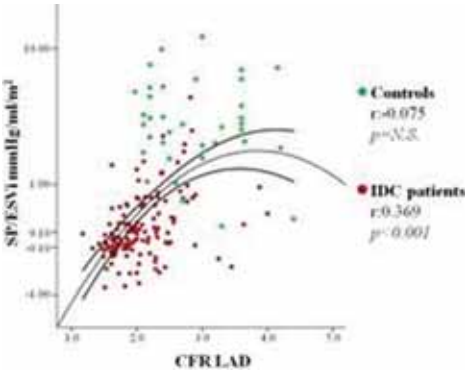

Figure 1

Conclusions: In IDC with impaired LV systolic function CFR was directly related to LV myocardial contractility, while this relationship disappeared in normal subjects.

P5598 | BEDSIDE

Exercise ventilatory power in heart failure patients: functional phenotypes definition by combining cardiopulmonary exercise testing with stress echocardiography

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Exercise Ventilatory Power (EVP; peak systolic blood pressure/exercise ventilation to CO2 production slope) is a new powerful prognostic marker that combines ventilator abnormalities with systemic hemodynamic during exercise. The phenotype and clinical relevance of patients with a worse EVP is broadly undefined and we aimed at this definition across a population of heart failure reduced ejection fraction (HFrEF) of different severity.
Methods: 77 HFrEF patients (mean age 65±11; male 70%; ischemic etiology 59%; NYHA class I, II, III and IV 23%, 33%, 31% and 13%, respectively; mean LVEF 34±9%) underwent cardiopulmonary exercise test (CPET) evaluation (ramp protocol on performed on a tilt-table cycleergometer) combined with simultaneous echocardiographic assessment.
Results: Patients were divided in 2 EVP classes (cutoff 3.5 mmHg) focusing on peak exercise echocardiographic variables.

Exercise ventilatory power in HF

	EVP ≥3.5 mmHg (n=61)	EVP <3.5 mmHg (n=16)	P value
Peak oxygen consumption (VO2), ml/kg/min	13.8±3.29	9.9±2.68	0.002
Rest LVEF (%)	33±8	28±10	0.03
Peak LVEF (%)	35±9	31±13	0.10
Rest cardiac output, (CO) l/min	3.85±1.18	3.20±1.50	0.12
Peak cardiac output, (CO) l/min	7.34±2.46	4.59±1.86	0.00006
Rest tricuspid annular systolic excursion (TAPSE), mm	18.5±4.06	13.6±3.18	0.00002
Peak tricuspid annular systolic excursion (TAPSE), mm	20.8±4.03	15.5±4.32	0.003
Rest pulmonary artery systolic pressure (PASP), mmHg	31.6±9.20	56.5±19.43	0.0001
Peak pulmonary artery systolic pressure (PASP), mmHg	54.3±14.36	74.5±23.47	0.004

Conclusions: A low EVP translates in a very unfavorable phenotype characterized by a lower peak VO2 and CO response at peak exercise. Remarkable impairment in right heart function and pulmonary hemodynamics were also peculiar of a low EVP. All the LV-pulmonary circulation- RV apparatus is abnormally involved in the exercise response of the EVP HFrEF phenotype.

P5599 | BENCH

Left ventricular diastolic dysfunction is associated with myocardial fibro-inflammation and elevated serum B-type natriuretic peptide

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Background: The STOP-HF study shows that community-based left ventricular dysfunction is predominantly diastolic. However, we have no specific therapies for asymptomatic left ventricular diastolic dysfunction (ALVDD), nor for its symptomatic equivalent, heart failure with preserved ejection fraction (HFpEF). More information on the pathophysiology could help the development of novel therapeutic approaches.
Aims: To compare serum biomarkers of inflammation, collagen turnover, extracellular matrix turnover, myocardial tissue evidence of fibrosis, macrophage activity and expression of associated genes in patients with and without ALVDD.
Methods: Myocardial tissue and peripheral serum samples were procured from 35 consecutive, consenting stable patients undergoing elective coronary artery bypass grafting surgery. All patients were screened with echocardiography before surgery and had a normal ejection fraction. They were further classified as having evidence of ALVDD or not based on elevated E/E' (>15) or E/E' 8-15 with at least one of E/a<0.5, DCT>280 ms, LVMI >122 g/m^2 in women, >149 g/m^2 men, LAVI>40 ml/m^2 and the presence of atrial fibrillation. Myocardial specimens were obtained adjacent to the venous cannulation site in the right atrial appendage. All subjects gave written informed consent to participate in the study.
Results: Patients were aged 67.4±9.8 years, 25 (69%) were male, all had symptomatic angina and 18 (53%) had hypertension, 5 (14%) had diabetes. ALVDD patients (n=10) had greater E/E' (12.5±2.6 vs. 8.4±2.0), greater LAVI (30.6±4.2 vs. 27.8±3.4), and more atrial fibrillation (70% vs 8%) than controls, all p<0.05. BNP levels were significantly higher in ALVDD patients (163±147 vs. 57±85, p<0.01) but no other blood biomarkers of inflammation, collagen turnover or extracellular matrix turnover differed between the groups. Tissue collagen volume fraction was significantly higher in the ALVDD group (55±7% vvs 47±8%) as was myocardial gene expression of collagen 1, collagen 3, MMP2, TNF alpha, Thy1, LOX and RPCP.
Conclusion: ALVDD is associated with elevated serum BNP, myocardial fibrosis and elevated expression of fibro-inflammatory genes in the myocardium in stable patients undergoing elective coronary artery bypass grafting surgery. Therapeutic strategies directed at modulating of fibrosis and inflammation in the heart may attenuate the progression of ALVDD to HFpEF.

P5600 | BEDSIDE

Effective symptomatic improvement by ivabradine treatment in chronic systolic heart failure patients in daily clinical practice is independent of beta blocker dose

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Objectives: The open-label, observational multicenter INTENSIfY study evaluated the effectiveness, tolerability, and effect on quality of life (QoL) of ivabradine treatment over a 4-month period in patients with chronic systolic heart failure (CHF).
Methods: Resting heart rate (HR), heart failure symptoms (NYHA class, signs of decompensation), BNP values and concomitant medication were documented in ambulatory CHF patients. Treatment with ivabradine twice daily was initiated for 4 months. QoL was evaluated by the EQ-5D patient questionnaire. A descriptive statistical analysis of the results was performed for three subgroups defined by beta blocker background dose (≥100%, 50% to 99%, and <50% of recommended target dose).
Results: In total 1956 patients (mean age 67±11.7 years) with CHF were analyzed. Etiology was ischemic for 62% of the cohort and the diagnosis had been known for more than 6 months for 85% of all patients. 78% received beta blockers. Other concomitant medication consisted e.g. of ACEI/ARB 83%, diuretics 61%, aldosterone antagonists 18%, cardiac glycosides 8%, aspirin 58% and statins 56%.
After 4 months of ivabradine treatment (mean dose 12.44 mg per day), the proportion of patients presenting with signs of decompensation and BNP >400 pg/ml decreased from 23% to 5% and from 54% to 27%, respectively. EQ-5D index also improved from 0.64±0.26 to 0.79±0.23, accompanied by a shift in NYHA classification towards lower grades. HR reduction by ivabradine was 18.1±12.3 bpm in the total study cohort. Overall response rate to treatment, defined as patient proportion with HR <70 bpm or HR reduction of ≥10 bpm at study end, was 89%. Treatment effects were similar in all three subgroups defined by beta blocker background dose (Table 1).

Table 1

$\Delta_{baseline-4\ months}$	<50% of beta-blocker target dose	50–99% of beta-blocker target dose	≥100% of beta-blocker target dose
Heart rate	−18±13 bpm (n=305)	−20±11 bpm (n=702)	−19.0±12 bpm (n=257)
NYHA III/IV patients	−23% (n=75)	−27% (n=200)	−24% (n=63)
Treatment responders	88% (n=268)	93% (n=649)	91% (n=233)

Conclusion: Over 4 months of treatment, ivabradine was effective in improving heart failure symptoms in CHF patients in daily clinical practice. Ivabradine also reduced BNP and improved QoL in these patients, accompanied by high treatment response rates. Treatment effects were independent of beta blocker background dose.

P5601 | BEDSIDE

The influence of ivabradine on circadian pattern of heart rate and ischemic episodes in patients with ischemic heart disease and heart failure

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Background: Ivabradine (Iv) belongs to new class of specific HR reducing without affectingmyocardial contractility, relaxation and peripheral vascular resistance. In this study we aimed to assess the influence of Iv treatment on circadian rhythm of HR and ischemic episodes in patients with HF.
Methods: 41 patients with HF (mean age 53.3±8.9) were enrolled in this study and treated with Iv 10 mg daily during 16 weeks. 24-hour ambulatory Holter monitoring ECG was registered before and after treatment. The circadian HR and ST-depression pattern were analyzes by SPSS 13.
Results: The obtained results have shown that the basic data of circadian variation of HR have two peaks- in 8.26 a.m. (with intervals between 7.02 and 10.35 a.m.) and in 6.34 p.m. (with intervals between 4.22 and 8.35 p.m.). The mesor of circadian rhythm was 96.9±16 b/min. HR circadian fluctuation range oscillated from 128 b/min to 87 b/min. The basic data of circadian variation of ST depression have two peaks: in 9.42 a.m. and in 5.38 p.m. The mesor and fluctuation range of ST depression were 28.1±14 and from 68 to 17 correspondingly). After treatment of Iv during 16 weeks two peaks of HR and ST depression circadian rhythm were remained. But the mesor and fluctuation range of HR circadian rhythm significantly decreased (67.8±8 b/min vs. 96.9±16 b/min and from 78 b/min to 56 b/min vs. from 128 b/min to 87 b/min.).
Conclusion: There is direct relationship between circadian rhythms of HR and ST depression episodes in patients with IHD and HF. Usage of Iv promotes to decrease the circadian mesor and fluctuation range of HR, and thereby improves the treatment target for patients with HF.

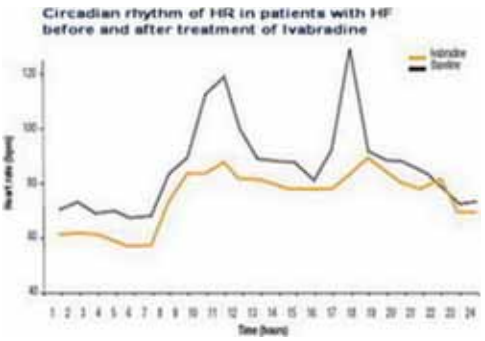

Figure 1. Circadian rhythm of HR.

P5602 | BEDSIDE

Performance of an integrated device diagnostic algorithm to predict the risk of worsening heart failure

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Background: Heart failure (HF) is a prevalent disease characterized by frequent hospital admissions and poor prognosis. The inability to adequately predict HF exacerbations remains the Achilles heel of HF management.
Aim: To test the performance of a novel HF risk stratification model, derived from daily measurements of multiple device diagnostic variables, to identify patients at risk for worsening HF.
Methods and results: Between Dec 2010 and May 2012 we recruited 63 HF pts (49 men) with reduced ejection fraction (EF). All pts had been implanted with an Optivol-enabled Medtronic CRT-D or ICD device at least 30 days prior to enrollment (mean time from implant to enrollment: 506±477 days). Study participants were prospectively followed for a minimum of 6 months. Demographic, clinical, device and outcome data were collected.
Mean age was 63±12 years, mean EF 29±11% and median NTproBNP 2154 ng/L (IQ: 814 to 4311 ng/L). At the time of inclusion, most pts had mild to moderate HF (52.5% NYHA II and 21.3% NYHA III) and suffered from ischemic cardiomyopathy (52.4%). Permanent AF was present in 14.3% pts.
HF events were classified as major or minor, depending on the need for hospitalization vs. presence of signs and/or symptoms of HF requiring ambulatory treatment. After a mean follow-up of 624±152 days, 88 episodes of HF were identified, with 41 major and 47 minor events. By combining device diagnostic data on intrathoracic impedance, AF burden, % CRT pacing, ventricular arrhythmia, night heart rate, heart rate variability and patient activity, the algorithm computed a daily HF risk score and categorized pts as being at low (L), medium (M) or high (H) risk for an event in the following 30 days (L: 0 < score ≤5; M: 5 < score ≤20; H: score >20). Compared to pts in the L group, pts in the M and H group had a relative risk (RR) of respectively 1.0 and 3.3 (95% CI: 0.6-1.9; 1.7-6.6) for worsening HF (minor+major events). Risk stratification was even better when only major HF events were considered, with a RR of 1.6 (95% CI: 0.6-4.4) and 4.3 (CI: 1.2-15.5) for pts in the M and H group, compared to the L group.
Conclusion: A HF risk model based on device diagnostic variables can identify pts at risk for worsening HF, especially those at risk for HF hospitalization.

P5603 | BENCH

Plasma galectin-3, a marker of myocardial fibrosis, is poorly related to the volume of myocardial scar in patients with heart failure

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Background: Increased myocardial expression of galectin-3 occurs after cardiac damage and may play a role in initiating scar formation and myocardial fibrosis.
Methods: Left ventricular (LV) volume, mass, ejection fraction (EF) and the extent of myocardial scar were measured using cardiovascular magnetic resonance (CMR) imaging in a random sample of patients with chronic heart failure, diagnosed clinically, confirmed by echocardiography (LVEF <40%) and/or NT-proBNP >400 pg/ml. Galectin-3, was measured within median of 2.17 months from the CMR scan [interquartile range (IQR) 0.95-6.44].
Results: Of 151 patients, the median age was 71 (IQR: 63-77) years, 130 (86%) were men, 106 (70%) had LVEF<50%. 107 had a history of ischaemic heart disease (IHD)/ myocardial infarction (MI). In the 87 patients with myocardial scar, the scar involved a median of 18 (IQR 12-23) % of left ventricular mass. Median plasma galectin-3 was 17.7 (range: 6.4-71.2; IQR: 13.0 - 23.7) ng/ml in patients with myocardial scar, and 15.2 (range: 6.8 - 45.5 IQR: 12.4 - 18.2) ng/ml [p=0.014] in patients without myocardial scar. Galectin-3 was poorly related to LV volumes, function, mass or extent of myocardial scar. There were weak associations between galectin-3 and serum creatinine (r=0.002; P=0.001) and log-transformed NT-proBNP (r=0.070; P=0.028), Galectin-3 was higher in women (P=0.038) and increased with New York Heart Association class.
Conclusion: The extent of myocardial scar assessed by CMRI is not strongly related to plasma galectin-3 in patients with chronic heart failure. The mechanism(s) leading to increased plasma concentrations of galectin-3 are not known.

HEART FAILURE BASICS

P5605 | BENCH
Chronic treatment with dihydroartemisinin, a Translationally Controlled Tumor Protein (TCTP) down-regulating agent, results in cardiac dysfunction in mice

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Objectives: Dihydroartemisinin (DHA), isolated from the traditional Chinese herb Artemisia annua, is an established agent for the treatment of malaria. In addition, recent studies both in vivo and in vitro have demonstrated the antitumor activity of DHA. DHA is reported to bind to translationally controlled tumor protein (TCTP), one of the anti-apoptotic proteins, and down-regulate its expression. Thus, TCTP is indicated to be involved in DHA-induced cell death. On the other hand, our recent results indicated that TCTP plays an important role in the prevention of cardiac apoptosis. Based on these findings, we hypothesize that chronic DHA-treatment may induce cardiac dysfunction through down-regulation of TCTP expression in the heart.
Methods and results: In neonatal rat ventricular cardiomyocytes, DHA treatment (50μM, 60 hours) induced apoptosis of cardiomyocytes (~3.25 fold higher than vehicle-treated control cells, $p<0.01$, N=4). Apoptosis was measured by Fluorescence Activated Cell Sorter (FACS) analysis with Annexin V and 7-AAD staining. The expression of TCTP was decreased (~33% lower than vehicle-treated control cells, $p<0.001$, N=4-8) after 48 hours treatment of DHA (50μM). Moreover, down-regulation of TCTP by siRNA enhanced apoptosis of cardiomyocytes (~1.38 fold higher than control siRNA-treated cells, $P<0.05$, N=4). To examine the effects of DHA on cardiac function in vivo, we performed echocardiography and cardiac catheterization after chronic DHA treatment (30 mg/kg/day, via intraperitoneal injection for 4 weeks) in wild type (WT) mice. Left ventricular ejection fraction (LVEF), LV dP/dt max were significantly decreased in DHA-treated mice compared with vehicle-treated control mice (CTRL) (LVEF: CTRL vs. DHA: 71.8±0.95% vs. 56.0±1.8%, $P<0.01$, N=4-6, LV dP/dt max: CTRL vs. DHA: 11358±2065 mmHg/sec vs. 7109±460 mmHg/sec, $P<0.01$, N=4-5). Consistently, the DHA-induced cardiac dysfunction was significantly rescued by cardiac specific over-expression of TCTP (TCTP transgenic mice: TG). (LVEF: WT vs. TG: 56.0±1.8% vs. 66.3±1.0%, $P<0.01$, N=5, LV dP/dt max: WT vs. TG: 7109±460 mmHg/sec vs. 9286±646 mmHg/sec, $P<0.05$, N=5).
Conclusions: These findings indicate that chronic DHA treatment results in cardiac dysfunction in mice. DHA-induced down-regulation of TCTP expression may be involved in the mechanism.

P5606 | BENCH
Simultaneous assessment of the impact of heart failure on protein and lipid synthesis using a new 2H2O-metabolic labeling method in a preclinical animal model

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Heart failure (HF) alters protein and lipid concentrations in plasma and tissues, however in vivo measurements of their rate of synthesis have been thus far hindered by the lack of adequate methodologies. We tested in dogs a new method to simultaneously measure rates of protein and lipid turnover using 2H2O (deuterated water) and subsequent endogenous labeling of 2H to amino acids and lipids. A loading dose of 2H2O was infused intravenously (15 ml/kg), followed by 72 hours of oral administration in the drinking water (5%) to dogs with advanced pacing-induced congestive HF (left ventricular end-diastolic pressure ≥25mmHg) and to normal controls (n=7/group). Blood samples were periodically drawn and left ventricular tissue was harvested at the end of the protocol. We initially focused on three cardiac and ten plasma major proteins, which were trypsinized after albumin depletion or gel electrophoresis, and peptide fragments analyzed by high resolution liquid chromatography-tandem mass spectrometry (MS). Protein synthesis was calculated from the time course of the rise in the enrichment of 2H in peptide isotopomers using specialized software. Total plasma cholesterol and fatty acids derivatized with trimethylchlorosilane were analyzed by gas chromatography–MS. Data are expressed as percent of newly synthesized molecules/hour over their respective total pools. Compared to control, in HF the turnover rate of cardiac proteins changed as follows (all $p<0.05$): heavy chain beta-myosin increased from 0.13±0.02 to 0.24±0.02%; adenine nucleotide translocase-1, a key enzyme involved in mitochondrial ATP production, decreased from 0.23±0.08 to 0.14±0.04%. The plasma albumin decreased from 0.29±0.03 to 0.16±0.01% and serotransferrin from 2.09±0.05 to 0.76±0.01%. Among the circulating lipids, palmitate displayed a reduced synthesis rate from 0.16±0.01 to 0.05±0.01% ($p<0.05$) in HF, while the reduction in cholesterol was at the limit of significance (1.45±0.21 vs 0.79±0.10%, p=0.05). In conclusion, HF slowed the synthesis of plasma proteins and lipids and had differential effects on myocardial contractile and metabolic proteins. These initial results are the first to show the potential of 2H2O-metabolic labeling for quantitative assessment of protein turnover in different stages of heart failure in a larger animal model and may help to develop additional molecular monitoring methodologies.

P5607 | SPOTLIGHT
Ox-LDL contributes to cardiomyocyte apoptosis and heart failure via lectin-like oxidized low-density lipoprotein receptor-1

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Purpose: Ox-LDL plasma level is a useful predictor of mortality in HF patients, however the precise mechanisms of ox-LDL on HF is poorly understood. This study investigates whether ox-LDL is involved in the development of HF and its mechanisms.
Methods: ox-LDL (200ng/kg. min) infused into mouse results in heart failure which was evaluated by echocardiography and BNP. To explore the mechanisms we find that Ox-LDL increases LOX-1 expression, leads to apoptosis of mouse heart and cultured cardiomyocytes, the signal pathways were determined by TUNEL assay, qPCR and western blot.
Results: 4 weeks after infusion of ox-LDL, the ratio of heart weight to body weight in ox-LDL treated mice was 6.91±0.32 mg/g vs 4.86±0.23 mg/g in sham-treated mice ($P<0.01$), LV internal dimension at end-diastole (LVIDd) was 3.78±0.13mm vs. 3.31±0.12mm ($P<0.01$), left ventricular fractional shortening (LVFS) was 25±2% vs. 44±1% ($P<0.01$), and plasma B type natriuretic peptide (BNP) was 4578±35pg/ml vs. 34±7pg/ml ($P<0.01$), which suggests that ox-LDL can cause significant heart failure of mice. Further studies find that ox-LDL increase LOX-1 expression and apoptosis in mouse hearts and cultured cardiomyocytes, ox-LDL not only activated caspase-3, but also increase Bax/Bcl-2 ratio of cardiomyocyte. Inhibition of LOX-1 significantly decreased ox-LDL-induced cardiomyocyte apoptosis, also improved heart failure of the mice.
Conclusions: Our results indicate that ox-LDL increases LOX-1 expression, Bax/Bcl-2 ratio of cardiomyocyte which may contribute to apoptosis of cardiomyocyte and mouse heart, eventually lead to heart failure of the mice.

P5608 | BENCH
NADPH oxidase and eNOS mediate Ang II up-regulation of nNOS protein expression

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Endothelial and neuronal nitric oxide synthases (eNOS & nNOS) are constitutively expressed in distinct subcellular locations within cardiomyocytes and exert diverse functions. In particular, nNOS protein expression and activity are significantly increased whereas eNOS protein expression is reduced in diseased heart or in the myocardium under stress. nNOS, in turn, protects the myocardium from pathologic progression and functional deterioration. So far, mechanism of nNOS up-regulation upon pathogenic stimuli is not fully understood. Recently, we have shown that angiotensin II (Ang II) treatment in vitro increases nNOS protein expression in rat left ventricular (LV) myocytes. Here, we aim to examine signaling pathways mediating Ang II up-regulation of nNOS in mammalian cardiac myocytes. Our results showed that Ang II (1 μM, 3 hrs) increased protein expression of nNOS (P=0.03, n=9) but eNOS protein expression remains unchanged in rat LV myocyte lysates. Type 1 Ang II receptor (AT1R) antagonist, losartan (1 μM), NADPH oxidase inhibitor, apocynin (100 μM) and superoxide scavenger, tiron (1 mM), abolished Ang II stimulation of nNOS protein expression and activity. Furthermore, Type 2 Ang II receptor (AT2R) antagonist, PD123319 (1 μM) also abolished Ang II stimulation of nNOS protein expression and activity, suggesting that AT1R may cross talk with AT2R in nNOS regulation. Indeed, whilst AT1R expression in the plasma membrane was reduced within 30 min, AT2R expression was increased without changing total AT1R and AT2R protein levels. Interestingly, losartan, apocynin and tiron abolished AT2R expression in plasma membrane, suggesting pivotal roles of AT1R and NADPH oxidase in AT2R membrane translocation and activation. In addition, Ang II significantly increased the phosphorylation of eNOS-Ser1177 and reduced eNOS-Thr495 (at 30 min) in LV myocytes. Pre-treatment of apocynin reduced eNOS-Ser1177, suggesting that AT1R/NADPH oxidase/ROS are upstream regulators of eNOS phosphorylation by Ang II. Importantly, eNOS inhibition with L-NAME diminished NO production in the presence and absence of Ang II and prevented AT2R translocation to the plasma membrane. L-NAME tended to reduce Ang II stimulation of nNOS protein expression in four cells (out of nine cells). Taken together, we provide novel evidences to demonstrate that Ang II up-regulates nNOS protein expression via AT1R/NADPH oxidase/ROS dependent-membrane translocation of AT2R. eNOS links AT1R regulation of AT2R membrane expression and activity. Our results suggest a novel cross talk between eNOS and nNOS in the myocardium under pathogenic stimuli.

P5609 | BEDSIDE
Role of sarcomeric gene polymorphisms on left ventricular dysfunction in coronary artery disease patients

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Purpose: In patients of coronary artery disease (CAD), left ventricular function is the most important determinant of prognosis. Many CAD patients develop left ventricle dysfunction (LVD), leading to congestive heart failure. Mutations in several genes including those encoding sarcomeric proteins such as MYBPC3, TNNT2, and TTN are common genetic cause of hereditary cardiac myopathies. An intronic 25-bp deletion in MYBPC3 at 3' region is associated with dilated (DCM) and hypertrophic (HCM) cardiomyopathies in Southeast Asia. Their role in genesis of LVD in CAD patients is not known. We sought to determine the role of MYBPC3 25bp, TNNT2 5bp and TNN 18bp insertion/deletion polymorphisms on LVD in CAD patients.
Methods: This case control study included a total of 1188 subjects including 988 angiographically confirmed CAD patients and 200 population matched controls. All patients had angiographically significant CAD and had coronary revascularization (coronary angioplasty or coronary bypass surgery) in the past. Left ventricular ejection fraction (LVEF) was analyzed by echocardiography. Patients with LVEF <45% were categorized as advanced LVD. MYBPC3 25bp, TNNT2 5bp and TNN 18bp insertion/deletion polymorphisms were determined by polymerase chain reaction. Results were compared between CAD patients and healthy controls and further in the CAD patients with LVEF less than 45% and more than 45%.
Results: Our results showed that MYBPC3 25bp deletion was significantly associated with CAD (p value = 0.003; OR = 4.08) as well as with LVD (p value = 0.031; OR=1.67). The TNNT2 5bp and TNN 18bp polymorphisms were not found to be associated with CAD (p value = 0.580, OR = 0.88; p value = 0.795, OR = 0.91 respectively) or LVD (p value = 0.146, OR = 1.35; p value = 0.935, OR=0.97 respectively) when compared to controls.
Conclusions: The frequency of MYBPC3 DW genotype and D allele was associated with LVD implying that genetic variants of MYBPC3 encoding mutant structural sarcomere protein could increase susceptibility to left ventricular dysfunction. Therefore, 25bp deletion in MYBPC3 may represent a genetic marker for cardiac failure in CAD patients.

P5610 | BENCH
Prostaglandin E2-EP4 plays a protective role against cardiac fibrosis

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Purpose: Cardiac fibrosis, which is not curable in current therapies, leads to heart failure and is associated with high morbidity. Previously, we have shown that cyclic AMP signaling attenuated cardiac fibrosis through inhibiting transformation of quiescent fibroblasts to active myofibroblasts. Although it is well known that prostaglandin E2 (PGE2) receptor EP4 acts via cyclic AMP and is abundantly expressed in the heart, the role of EP4 in cardiac fibrosis is not fully understood. In this study, we assessed the hypothesis that PGE2-EP4 signaling inhibits cardiac fibrosis.
Methods: Cardiac fibroblasts (CFs) and cardiomyocytes (CMs) were isolated from global knockout of EP4 (EP4+/–) and wild type (EP4+/+) male littermate mice (3 or 4-month-old) or 5-week-old male rats by Langendorff collagenase perfusion. Expression levels of mRNAs of EP4 and connective tissue growth factor (CTGF) which enhances myofibroblast activation and fibrosis were assessed by quantitative RT-PCR. Western blotting was performed to quantify CTGF protein expression. Cardiac fibrosis was induced by 7 days of systemic infusion of angiotensin II (AngII) (1.0μg/kg/min) in EP4+/– and EP4+/+, and the mice overexpressing EP4 only in CMs using the Cre-loxP system under SM22 promoter. Picrosirius red stain-positive fibrotic area was quantified by a color extraction method.
Results: In wild type mice, expression level of EP4 mRNA was significantly higher in CFs than in CMs (9.3±0.1-fold, n=4, p<0.05). When rat CFs were stimulated with PGE2 or EP4 agonist (CAY 10580) at 1μM, CTGF protein expression was decreased (0.38±0.1-fold or 0.40±0.2-fold, respectively, n=4). Conversely, in CFs of EP4+/– where EP4 mRNA expression was decreased by 58±1% (n=7, p<0.05), expression level of CTGF mRNA was slightly higher compared to EP4+/+ CFs (1.6±0.2-fold, p=0.07, respectively, n=5). Systemic administration of AngII decreased EP4 mRNA in both EP4+/– and EP4+/+ mice (0.38±0.05-fold and 0.53±0.2 -fold, respectively, n=3). In this fibrosis model, CTGF mRNA expression and cardiac fibrosis were increased to a greater extent in EP4+/– than in EP4+/+ mice (3.1±0.9-fold, n=3, and 4.6±1.7-fold, n=4, p<0.05). On the other hand, in the mice overexpressing EP4 only in CMs, AngII-induced fibrosis was not decreased compared to non-transgenic mice, suggesting smaller contribution of CMs than CFs in cardiac fibrosis.
Conclusions: Endogenous PGE2-EP4 signaling in CFs may have a protective role against cardiac fibrosis possibly through inhibiting CTGF-mediated activation of myofibroblasts.

P5611 | BENCH
Baroreflex failure induces volume supersensitivity and predisposes to pulmonary edema

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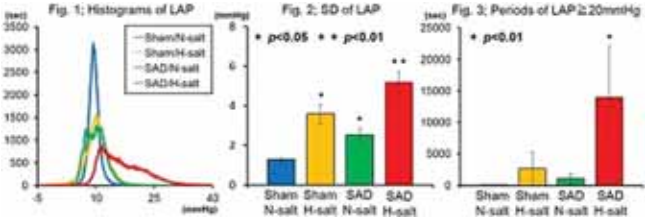
Purpose: Patients with heart failure with preserved ejection fraction (HFpEF) frequently suffer from pulmonary edema with little weight gain indicating underlying a volume supersensitive mechanism. These patients often have baroreflex dysfunction and salt-sensitive hypertension. We recently demonstrated that baroreflex failure resulted in striking volume intolerance (J Cardiac Failure, 2014). In this study, we examined how baroreflex failure impacts on daily fluctuations of left atrial pressure (LAP) in hypertensive rats with high salt diet.
Methods: We allocated 14 weeks old spontaneously hypertensive rats (SHR) into 2 groups. We conducted sinoarotic denervation (SAD, n=10) to abolish baroreflex or sham operation (Sham, n=10). In the following week, we implanted a telemetry system to measure arterial pressure (AP) and LAP. 1 week after the 2nd surgery, 2 groups were subjected to either normal (N-salt) or high salt diet (H-salt, 8% NaCl). We recorded 24-hour histograms of AP and LAP in 17 weeks of age.
Results: H-salt increased AP both in Sham (167.9±3.6 vs. 150.5±6.2 mmHg) and SAD (176.5±12.2 vs. 146.4±1.9 mmHg). SAD significantly increased the standard deviations (SD) of AP both in N-Salt (17.2±4.6 vs. 9.5±0.9 mmHg, p<0.05) and in H-Salt (21.5±5.3 vs. 13.0±1.4 mmHg, p<0.05). In contrast, only SAD/H-salt increased mean LAP (SAD/H-salt 14.4±2.3 vs. Sham/N-salt 11.0±1.5 mmHg, p<0.05, Fig. 1) with marked increases in their SDs (Fig. 2). Furthermore SAD/H-salt strikingly prolonged the high LAP period (≧20 mmHg, Fig. 3) that accounted for more than 20% of 24 hours.



Conclusion: Baroreflex failure markedly increases daily fluctuations of LAP and prolongs the period of high LAP indicating that baroreflex failure would play a crucial role in the pathogenesis of pulmonary edema in patients with HFpEF.

P5612 | BENCH
ATP synthase subunit alpha and left ventricular mass in ischemic cardiomyopathy. A mitochondrial proteomic approach used on human cardiac tissue

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Purpose: Mitochondrial dysfunction plays an important role in the development of ischemic cardiomyopathy (ICM). We hypothesize that heart failure of ischemic origin induces changes in the proteome of this organelle. The objective of this study is to analyze the protein profile of the mitochondria, isolated and purified from cardiac tissue of patients with ICM undergoing heart transplant.
Methods: Mitochondrial extracts from 16 hearts (left ventricle) have been analyzed by two-dimensional electrophoresis using DIGE, [8 patients with ICM and 8 non-pathological donors, used as a control (CNT)]. To identify the proteins of interest we use mass spectrometry. In addition, to further validate results we increased the number of samples (n=24) and we performed western blot, immunofluorescence, immunohistochemistry and SRM techniques.
Results: We isolated mitochondria from left ventricular (LV) samples of explanted hearts of ICM patients (n=8) and control donors (n=8) and used a proteomic approach to investigate the variations in mitochondrial protein expression. We found that most of the altered proteins were involved in cardiac energy metabolism (82%). We focused on ATPA, which is involved in energy production, and DLDH, implicated in substrate utilization, and observed that these molecules were overexpressed and that the changes detected in the processes mediated by these proteins were closely related. Notably, we found that ATPA overexpression was associated with reduction in LV mass (r=-0.74, P<0.01). All of these changes were validated using classical techniques and by using novel and precise selected reaction monitoring analysis and an RNA sequencing approach, with the total heart samples being increased to 24.
Conclusions: This study provides key insights that enhance our understanding of the cellular mechanisms related to the pathophysiology of ICM and could lead to the development of etiology-specific heart failure therapies. ATPA could serve as a molecular target suitable for new therapeutic interventions in ICM patients.

P5613 | BENCH
Aging impairs adaptive cardiac hypertrophy to exercise via Akt/mTOR-dependent autophagy

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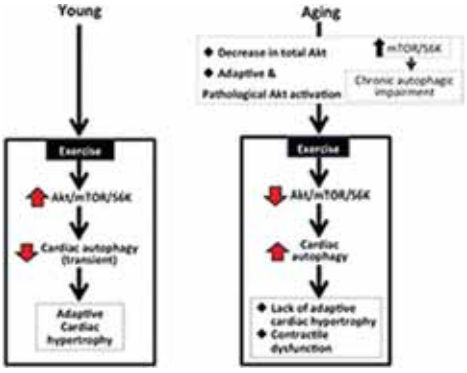
Purpose: Aging causes left-ventricular (LV) remodeling and susceptibility to heart failure (HF). Sustained exercise (EX) ameliorates HF; however, it is unclear EX may be beneficial for the aging-related HF. Because of the pivotal role of protein kinase Akt in aging, we hypothesized whether EX may modulate HF in aging via Akt axis.
Methods: Male 6-month-old genetic senescence -Prone (genP) & -Resistant (genR) of SAM strain mice were subjected to EX [60-min treadmill for 6 months]. The same protocol was tested on the acquired aging (12 m/o) mice [wild (agedC57) and Akt knockout (agedAktKO)] and young (14 w/o, youngC57) counterpart.
Results: At baseline, cardiac geometry of genP exhibited LV wall thinning. Systolic function of both strains was preserved. After EX, body and heart weight of genR were increased, but EX had no influence on those genP. EX promoted cardiac hypertrophy and increased capillary density in genR, but absent in genP, suggesting genP lacks physiological LV remodeling. EX impaired systolic function of genP [EF (%): 68.9±1.5 vs 74.3±1.2 at baseline]. Cardiac Akt/mTOR/S6K activity was enhanced by EX in genR. Unexpectedly, genP-CON exhibited basal increase in the Akt/mTOR/S6K activity, which was reversed by EX. The genP-CON exhibited impaired cardiac autophagy, which was reversed by EX in an Akt-mTOR-S6K dependent manner.
The agedC57 exhibited the same trend of insusceptiblity to the EX-induced LV hypertrophy. Consistently, agedAktKO exhibited both systolic dysfunction [EF (%): 61.3±1.0] and absence of hypertrophy.



Conclusions: EX-induced adaptive LV hypertrophy requires Akt activation. Aging promotes chronic and pathological Akt activation in heart, which promotes autophagic impairments. EX triggers to reverse Akt/mTOR/S6K-dependent autophagy.

P5614 | BENCH
Chromogranin B: A signal of myocardial remodeling in chronic ischemic heart failure

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Purpose: Cardiac myocyte apoptosis and hyperthrophy are important mechanisms of ventricular remodeling which may lead to heart failure (HF) in general accompanied by increased brain natriuretic peptide (BNP) production.
Chromogranins are calcium storage proteins which activate inositol 1,4,5-trisphosphate receptors (InsP3Rs). Chromogranin B (CGB), rather than CGA, is involved in cardiomyocyte signaling cascades that mediate cardiac hypertrophy and HF by the regulation of an InsP3R and calcium dependent pathway. However, it still is unknown if CGB is regulated differently in acute and chronic HF (aHF, cHF) and if this parallels cardiac BNP production, as would be assumed from previous studies. Therefore, we studied rat ventricular CGB, CGA and BNP production in aHF and cHF.
Methods: Male wistar rats were subjected to MI by LAD ligation for 24 hours (aHF) or 14 days (cHF) (LIG) and compared to sham operated controls (CO). Echocardiography was performed before and 24 hours or 2 weeks after MI and fractional shortening (FS) was calculated. Protein expression was quantified by Westernblot analysis of samples taken from the non-ischemic left ventricular posterior wall (PoLV). In cryo-sections, the presence of apoptosis and hyperthrophy was documented by (immuno-)histochemistry. Serum BNP was quantified by ELISA.
Results: In aHF, LIG animals showed significantly reduced FS (LIG 35% vs. CO 63%) with BNP serum levels significantly elevated (LIG 5040 vs. CO 3090 fmol/ml). In contrast, no significant change in CGB or CGA PoLV expression was observed in LIG vs. CO animals.
In cHF, LIG animals showed a significant increase in the heart/body weight ratios compared to CO as a sign of significant HF. FS was significantly impaired in the LIG group (LIG 31% vs. CO 66%). Of note, a significant increase in PoLV CGB expression was observed (LIG 146% of CO) paralleling persistently elevated BNP serum levels (LIG 2402 vs. CO 1430 fmol/ml). In contrast to CGB, PoLV CGA expression in LIG vs. CO was unaltered.
As part of the remodeling process, we documented significantly increased numbers of PoLV apoptotic cardiomyocytes in LIG vs. CO animals in aHF and cHF.
Conclusion: Dissociation of time courses in the activation of BNP and CGB suggests sequential or separate signaling mechanisms in aHF and cHF after MI. It indicates that CGB may be a signal of myocardial remodeling in cHF. Of note, CGA seems not to be regulated in ischemic aHF nor cHF. Further studies are warranted to completely understand the role CGB plays in myocardial remodeling mechanisms with the ultimate goal to aid in diagnosis and treatment of HF patients.

P5615 | BEDSIDE
Telomere length as predictor for new onset heart failure

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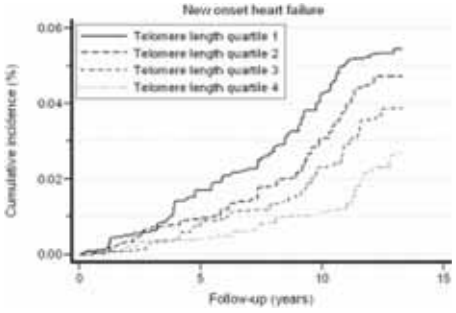
Purpose: Telomeres protect against chromosomal instability and are considered a marker for biological age. Accelerated telomere shortening has been associated with a variety of cardiovascular diseases. In this study, we hypothesized that telomere length is associated with new onset heart failure.
Methods: In 1997, the Prevention of REnal and Vascular ENd-stage Disease (PREVEND) study was initiated and included 8,592 subjects. We measured telomere length in leukocytes of 8,053 subjects from PREVEND, of whom 351 subjects have developed heart failure during a median follow-up of 12.5 years, and divided telomere lengths in quartiles for statistical purposes.
Results: We found that baseline telomere length was significantly shorter in subjects developing heart failure compared to subjects without new onset heart failure ($P<0.001$). Compared to the longest telomere length quartile, the shortest length quartile was associated with increased risk of new onset heart failure (see figure, quartile 1 contains shortest telomeres, hazard ratio 2.26, 95%CI 1.42-3.61, P=0.001), mortality (hazard ratio 2.23, 95%CI 1.62-3.06, $P<0.001$) and the occurrence of cardiovascular events (hazard ratio 2.17, 95%CI 1.60-2.96, $P<0.001$). These relationships were, however, not independent of chronological age.



Conclusion: In the PREVEND study cohort, healthy individuals who developed new onset heart failure during follow-up are characterized by shorter leukocyte telomeres, albeit not independent of date of birth, compared to heart failure-free subjects.

P5616 | BEDSIDE
Circulating CD14++CD16+ monocyte subsets as a surrogate marker of inflammatory activity in patients with cardiac sarcoidosis

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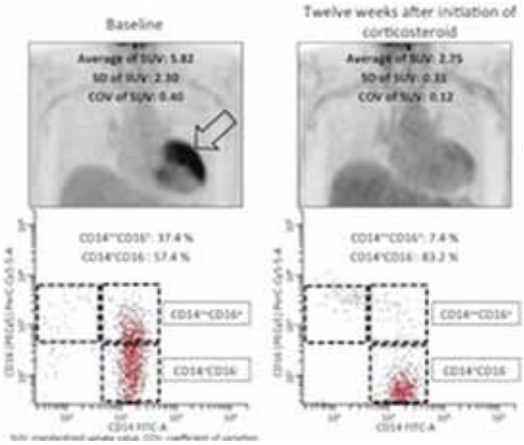
Aims: The aim of this study was to evaluate whether specific monocyte subsets could serve as surrogate markers of disease activity in cardiac sarcoidosis (CS) evaluated by 18F-fluoro-2-deoxyglucose positron emission tomography (18F-FDG PET).
Methods and results: Twenty-five patients with CS (8 men, 17 women; mean age, 60±9 years) diagnosed according to consensus criteria were enrolled in this study. We divided CS patients into two groups, known CS receiving corticosteroid therapy (Rx (+); n=13) and new-onset CS (Rx (–); n=12), and analyzed 3 distinct monocyte subsets (CD14+CD16-, CD14++CD16+, and CD14+-CD16+). Monocyte subsets were also analyzed in 7 Rx (–) patients before and 12 weeks after starting corticosteroid therapy. Inflammatory activity was quantified by 18F-FDG PET using the coefficient of variation (COV) of the standardized uptake value (SUV). The proportion of CD14++CD16+ monocytes in Rx (+) patients (10.8 [0.2 to 23.5] %) was significantly lower than those in Rx (–) patients (25.2 [17.7 to 38.4] %, P=0.001). After corticosteroid therapy, the COV of the SUV was signif-



Images of FDG PET and monocyte subsets.

icantly improved from 0.32 [0.14 to 0.46] to 0.14 [0.10 to 0.22] (P=0.011). The proportion of CD 14++16+ monocytes showed a significant decrease from 25.8 [17.7 to 38.4] % to 9.7 [2.5 to 16.8] % (P=0.002). The decrease in the proportion of CD 14++16+ monocytes was significantly correlated with the decrease in the COV of the SUV (r=0.693, P=0.006).
Conclusion: CD 14++16+ monocytes are a possible surrogate marker of inflammatory activity in CS.

HEART FAILURE RISK

P5618 | BEDSIDE
Clinical charcteristics of < 90 day readmitted patients in the Korean Acute Heart Failure (KorAHF) registry

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Purpose: Readmission after hospitalization for HF is common. However, there are limited data describing patterns of follow-up after HF hospitalization and its association with readmission rates.
Methods: The patients hospitalized for acute HF syndrome in ten regionally-representative tertiary university hosptials have been consecutively enrolled 4183 patients between March, 2011 and July, 2013. The study is expected to complete the enrollment of 4,500 patients in 2013 and to follow-up until 2016. The aim of the present study was to decribe the clinical characteristics and outcomes of <90-day readmitted patients in this Korean Acute Heart Failure (KorAHF) registry.
Results: A total <90-day readmitted 955 patients among 4183 patients were enrolled in this analysis. At the hospital level, the mean age was 69.9±13.7 years; 52.8% were male; 42.3% were de novo HF; 63.8% had hypertension; 32% had ischemic heart disease. 88.6% of patients presented with NYHA III-IV dyspnea and the mean LVEF was 39.0±15.6%. Ischemia was both the leading cause (37.7%) and the most frequent aggravating factor (15.3%). Serum creatine level was 1.6±1.6mg/dL; Hemoglobin was 11.9±2.3g/dL; BNP and NT-proBNP level was 1457.6±1385.6 and 10458.2±10685.7 pg/mL. Angiotensin converting enzyme inhibitors/angiotensin receptor blockers and beta-blockers were prescribed at discharge in 66.0% and 44.7% of the patients. Aldosterone antagonists were prescribed at discharge in 52.3% of the patients. The mean length of hospital stay was 15.9±19.8 days and 90-day mortality was 10.1%. The readmitted patients group had significantly worse past medical history and laboratory findings. Also, they had significantly higher mortality and length of hospital stay (Table 1).

Table 1. Comparison of clinical outcomes and cost between two groups

		Readmitted*	Non-admitted*	p-value
Outcome	Hospital duration (d)	12.7±14.3	15.9±19.9	<0.001
	Binary discharge kind death or improve	25 (0.9)	28 (2.9)	<0.001
	Mortality	96 (10.1)	90 (3.3)	<0.001

Conclusions: Clinical characteristics at hospital level and 90-day outcomes of readmitted patients from KorAHF registry were described. Readmitted patients group had a wore clinical characteristics and outcome compared to non-readmitted patients group.

P5619 | BEDSIDE
Calcium supplementation in patients with chronic heart failure: Is it safe?

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Purpose: Recent observational studies suggest that calcium supplementation in healthy individuals is associated with adverse cardiovascular outcomes but whether the risk is further elevated in patients with existant heart disease is unknown. We aimed to investigate whether calcium supplements are associated with adverse outcomes in patients with chronic heart failure (CHF).
Methods: Data were analysed from 1053 patients with CHF (LVEF≤45%) who were enrolled in a prospective observational study for the occurrence of hospitalisation and mortality. Using pseudonymised electronic general practice patient records, outcomes were compared between patients who were and were not prescribed calcium supplementation. CHF patients with diabetes mellitus (DM) are at highest overall risk, so we prespecified a subgroup analysis of patients with DM.
Results: During a mean follow-up of 3.2 years, there were 296 all-cause deaths and 181 cardiovascular deaths. Calcium supplement users (n=170 (16.1%)) were older, and were more likely to be women, diabetic and more symptomatic (higher NYHA class). They had lower haemoglobin and worse renal function. They were less frequently prescribed ACE inhibitors, angiotensin receptor blockers and Beta-blockers. Calcium supplementation was associated with all-cause hospitalisation (odds ratio (OR) 1.60 (95% CI 1.12-2.30)), cardiovascular hospitalisation (OR 1.65 (95% CI 1.06-2.58)) and heart failure hospitalisation (OR 1.90 (95% CI 1.05-3.45)) but these associations were not statistically significant after adjustment for confounders.
In CHF patients with DM (n=275 (26.1%)), calcium users (n=55 (20%)) were more likely to be female, have lower haemoglobin and albumin, higher blood pressure and worse renal function compared to nonusers with DM. Calcium supplementation in diabetics was associated with an even greater trend to increased risk of all-cause (OR 2.03 (95% CI 1.11-3.72)), cardiovascular (OR 2.33 (95% CI 1.17-4.63)), and heart failure (OR 2.50 (95% CI 1.04-6.00)) hospitalisation, and after adjustment, this remained significant for all-cause hospitalisation (OR 2.13 (95% CI 1.04-4.38)).
Conclusions: Patients with CHF are frequently prescribed calcium supplementation, despite no evidence from randomised, placebo controlled trials. Our data reveal a 50% higher hospitalisation rate, and in those at highest risk (those with DM), the risk of hospitalisation is more than doubled, and is statistically significant after correction for other factors. A larger cohort is needed to confirm the preliminary findings in this population.

P5620 | BEDSIDE
Growth differentiation factor-15 (GDF-15) predicts cardiac events and echocardiographic response to cardiac resynchronization therapy (CRT) in chronic heart failure

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Aim: As the response to Cardiac Resynchronization Therapy (CRT) varies, many predictors of beneficial outcome have been proposed. The aim of this study is to determine whether growth differentiation factor-15 (GDF-15) predicts cardiac events after cardiac resynchronization therapy (CRT) in 12 months of clinical observation. GDF-15 is a member of the transforming growth factor-b (TGF-b) cytokine superfamily, with impact on cell survival, proliferation, and differentiation. In patients with heart failure, GDF-15 is an independent predictor of mortality.
Methods and outcomes: 51 patients (pts) with heart failure [age 63±8.7 years (mean±SD)], mean left ventricular ejection fraction (LVEF) (24.8±5.7%), New York Class Association (NYHA) class III (n=37) or IV (n=5), and QRS (165.6+21.2 ms) undergoing CRT were enrolled. All pts had clinical, echocardiographic evaluation and followed up for a maximum of 12±2 months for events. Serum GDF-15 was measured before implantation. All pts were scheduled for echocardiographic evaluation after 6±2 months. Cardiovascular event was considered as a composite end point (total mortality, heart failure hospitalization, or adequate ICD shock). Response to CRT was defined as 25% increase in LVEF as compared to entry value at 6 months' evaluation.
Results: There were 17 events over 12 month's follow-up (3 mortal episode's +7 hospitalization +7 ICD shock). Patients who met the combined adverse endpoint presented with (4183±882 pg/ml) GDF15 concentration as compared to event-free subset (3439±643 pg/ml, p=0.001). Mean ejection fraction overall improved to (34.4±9.3%, p<0.001) at follow up. Echocardiographic responders to CRT represented 49% of all enrolled pts. Patients who met the criteria for echocardiographic response presented with (3350±739 pg/ml) GDF15 concentration as compared to event-free subset (4011±740 pg/ml, p=0.01). The threshold value for responders was (GDF15 ≤4021,5 pg./ml) [Area Under Curve (AUC): 0,722, Positive Predictive Value (PPV): 0,629, Sensitivity: 0,880, Specificity: 0,500, Odds Ratios (OR): 7,333, 95% Confidential Interval (CI) 1,754-30,657, p=0,003]. In stepwise logistic regression model, pre-implantation serum GDF-15 level was an independent predictors of echocardiographic response to CRT (p=0.025) and occurrence of cardiac event (combined endpoint of mortality, hospitalization, ICD intervention) (p=0.001).
Conclusion: Serum GDF-15 concentration measured before implantation of CRT predicts response to CRT and occurrence of cardiac events in patient's with HF undergoing CRT-D therapy during 12months follow up.

P5621 | BEDSIDE

A role of serum sodium to urea nitrogen ratio as a brief prognostic bio-marker in patients with diuretic-resistant congestive heart failure

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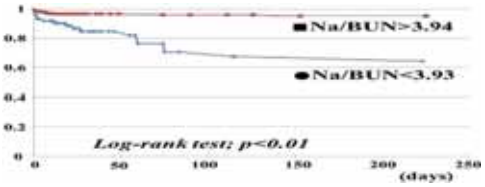
Background: Pathophysiology is complex and long-term prognosis is hard to predict in diuretic-resistant congestive heart failure (DR-CHF). Recently, both an increase in serum levels of urea nitrogen (BUN) and a decrease in serum levels of sodium (Na) during hospitalization have been proposed as a new prognostic impact in patients (pts) with DR-CHF, however, brief and predictive bio-markers are still unknown.
Purpose and method: To examine the role of Na (139±5mEq/L), BUN (30 ±20mg/dl) and Na/BUN ratio (5.8±2.8) at hospitalization on long-term prognosis, consecutive 287 CHF pts (78±13 years old; 162 male aged 74±14, 125 female aged 83.9±8.4) requiring intravenous administration of various diuretic and vaso-active agents at intensive care unit were examined and followed retrospectively. Based on the average values and previous reports, cutoff point was estimated on each parameter, and cumulative survival rate was examined by log-rank test.



Cumulative survival curve.

Results and conclusion: Prognostic impact was observed in pts with low Na (<139mEq/L; p=0.03[chi-square test],sensitivity 0.63; specificity 0.41; positive predictive value 0.14; negative predictive value 0.94), with high BUN (>30mg/dl; p=0.0005; 0.63; 0.70; 0.18; 0.95) and with low Na/BUN (<3.93; p<0.00001; 0.64; 0.77; 0.21; 0.96), respectively. The low Na/BUN ratio of less than 3.93 was found to be a most predictive marker for long-term survival (Figure, p<0.01). Therefore, the combination of fluid volume (Na) and neurohormonal (BUN) factors (Na/BUN ratio) may be a candidate for additional brief prognostic marker in diuretic-resistant CHF.

P5622 | BEDSIDE

Ultrasound assessment of jugular vein distensibility in patients with heart failure: prognostic significance. A report from the SICA-HF study

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Aims: Jugular venous distension reflects increased right atrial pressure and is a classical sign of heart failure (HF). However, its clinical assessment may be difficult.
Methods: Ambulatory patients with HF and control subjects enrolled in the SICA-HF study were assessed. Internal jugular vein diameter (JVD) was measured using a linear high-frequency ultrasound probe (10 MHz) at rest, during a Valsalva manoeuvre and during deep inspiration. JVD ratio was calculated as the diameter during Valsalva to that at rest.
Results: 311 patients (median (inter-quartile range[IQR]) age 71 (64-77) years, mean left ventricular ejection fraction 42±12%, median NT-proBNP 979 (IQR: 441-2007) ng/l) and 66 controls were included. JVD (median and IQR range) at rest was smaller in controls (0.16 (0.14-0.20) cm) than in patients with HF (0.23 (0.17-0.33) cm; p<0.001) but similar during Valsalva (1.03 (0.90-1.16) cm vs 1.08 (0.90-1.25) cm; p=0.28). Consequently, JVD ratio was greater in controls (6.3 (4.9-7.6)) than in patients (4.5 (2.9-6.1); p<0.001).
During a median FU of 516 (IQR: 335-622) days, 48 patients with HF died or were hospitalized for heart failure. Different multivariable models were tested. Amongst clinical, echocardiographic or biochemical variables, only NTproBNP and ultrasound assessment of internal jugular vein (either at rest, JVD ratio or deep inspiration, but not JVD during Valsalva) provided independent prognostic information. Compared to those in lowest tercile, HF patients in the highest tercile of JVD ratio had 10-fold greater risk of an adverse event (HR: 10.05, 95% CI: 3.07-32.93).
Conclusions: Echocardiographic assessment of internal jugular vein identifies ambulatory patients with heart failure who have a high risk of an adverse outcome. Greater JVD diameter at rest or during deep inspiration or smaller JVD ratio provide similar prognostic information.

P5623 | BEDSIDE

Cardio-liver syndrome in acute decompensated heart failure hospitalizations: definition and prognostic evaluation

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Liver dysfunction (LD) may develop in patients (p) hospitalized for acute decompensated heart failure (ADHF). There is no consensus on LD diagnostic criteria in this setting.
Aims: To characterize LD in ADHF, propose a Cardio-Liver syndrome (CLS) definition and describe outcome.
Methods: Demographic, clinical and biochemical data were recorded at admission. CLS was defined as an admission liver function test impairment characterized by aspartate aminotransferase ≥60 IU/L, alanine aminotransferase ≥75 IU/L; alkaline phosphatase ≥225 IU/L, total Bilirubin ≥1.5 mg/dl or gamma-glutamyl transferase ≥100 IU/L. Length of stay (LOS), mortality and readmission rates at 90 days (d).
Results: 454 consecutive P were admitted between July 2011 and December 2013. CLS was identified in 51%. Systolic pressure at admission (124 vs 139 mmHg; p<0.001) and left ventricular ejection fraction were lower in CLS (36 vs 42%; p<0.001). Considering clinical presentation, right-sided heart failure (RF) (35 vs 22%; p=0.002) and hypoperfusion were more frequent in CLS (24 vs 5.6%; p<0.001), as inotropic use and WHF (31 vs 9%; p<0.001) and (27 vs 11.5%; p<0.001). Right ventricular systolic pressure (53 vs 46 mmHg; p<0.001) and central venous pressure (14 vs 9 mmHg; p<0.001) were higher in CLS. There was a relationship among RD, thyroid dysfunction (THYR) and CLS (50 vs 41%; p=0.04 for RD; and 75 vs 62%; p=0.01 for THYR). Diuretic resistance (13 vs 5.4%; p=0.01) and previous Furosemide doses were higher in CLS (35 vs 16 mg; p<0.001). LOS was longer in CLS (7 vs 5 d; p<0.001).
Previous admissions were more frequent in CLS (56 vs 33%; p<0.001). Time to readmission tended to be shorter in CLS (48 vs 82 d; p=NS).
In multivariate analysis hypoperfusion (OR 3.1; 95%CI 1.2-8; p=0.01), RF (OR 2.8; 95%CI 1.6-4.8; p<0.001), inotropic drug use (OR 2.1; 95%CI 1.01-4.6; p=0.04) and low T3 levels (OR 2; 95%CI 1.2-3.5; p=0.01) predicted CLS development.
In-hospital (12.6 vs 5.4%; OR 2.5; 95%CI 1.2-5; p=0.01) and 90 d follow-up mortality were higher for CLS (16.2 vs 5.9%; OR 3; 95%CI 1.-6; p<0.001). Although CLS was not independently related to in-hospital mortality, it was strongly associated with 90 d follow-up mortality (OR 3.1; 95%CI 1.3-7.5; p=0.01).
Conclusions: CLS was prevalent in ADHF. It was associated with thyroid disorders, biventricular dysfunction, hemodynamic derrangement, longer hospitalizations and higher mortality, particularly mid-term.
Early organ dysfunction in ADHF should be emphasized for outcome prediction. Since CLS may occur with different patterns, it is important to further characterize this clinical syndrome.

P5624 | BEDSIDE

High-sensitivity cardiac troponin T predicts non-cardiac mortality in Heart Failure

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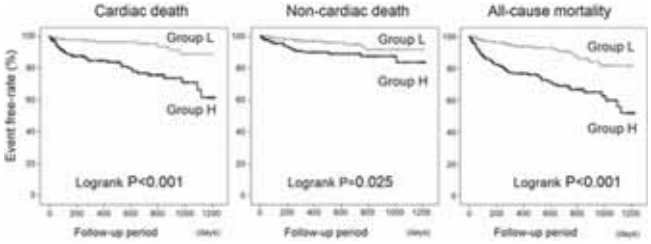
Background: Cardiac troponins are independent predictors of cardiac mortality in patients with heart failure (HF). Recently, elevation of troponins has been described in non-cardiac diseases such as stroke and infection, among others. However, it still remains unclear whether high-sensitive troponin T (hs-TnT) predicts non-cardiac mortality in HF patients.
Methods and results: Consecutive 444 HF patients admitted to our hospital for the treatment of decompensated HF were divided into 2 groups based on median hs-TnT: Group L (<0.028 ng/ml, n=220) and Group H (≥0.028, n=224). We compared all-cause mortality and echocardiographic findings between the two groups. In the follow-up period (mean 472 days), 77 deaths (49 cardiac deaths and 28 non-cardiac deaths (cancer, n=6; infection/sepsis, n=6; respiratory failure and/or pneumonia, n=5; stroke, n=4; digestive hemorrhage, n=3; renal failure, n=3; and aortic aneurysm, n=1)) were observed. The event-free survival (cardiac death, non-cardiac death and all-cause death) was significantly higher in Group L than in Group H (Figure). In the multivariate Cox proportional hazard analysis, a high hs-TnT was found to be an independent predictor of cardiac death (P<0.001), non-cardiac death (P=0.042) and all-cause mortality (P<0.001) in HF patients after adjusting for other known risk factors. Regarding echocardiographic paremeters, left ventricular wall thickness was higher (P<0.001), and left ventricular ejection fraction was lower (P=0.011) in Group H than in Group L.



Kaplan-Meier curves for Groups H and L.

Conclusions: Hs-TnT is an independent predictor not only of cardiac mortality, but also non-cardiac mortality in HF patients.

P5625 | BEDSIDE
Left ventricular ejection fraction during acute coronary syndrome has different association with mortality in women and men (From the ABC-3 Study on Acute Coronary Syndrome)*

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Purpose: To investigate sex-based differences in the association between left ventricular ejection fraction (LVEF) and 15-year mortality after acute coronary syndrome (ACS).
Methods: The ABC-3 Study on Acute Coronary Syndrome is an ongoing, prospective investigation designed to reflect, as closely as possible, an unbiased population of patients with ACS. The present analysis includes 504 patients. Baseline, clinical and laboratory data were obtained within the first 3 days of hospitalization. Measured variables were analyzed as quartiles of increasing values. Interaction between gender and LVEF was studied first by means of relative risks (RR) and Mantel-Haenszel test of homogeneity (with $p<0.05$ indicating dis-homogeneity of the RR), then using Cox surviving regressions including an interaction term and adjusting for age. All analysis were made both for early mortality (3rd to 66th day after admission) and long-term cardiovascular (CV) mortality (67th day to 15th year).
Results: Median age was 66 (IQ 58-73) years, female were 28%, LVEF was 52 (IQ 45-60)%, NSTEMI were 37%. All the patients were followed up to 15 years of observation or time to death. Of them, 48 had died in the early- and 162 in the long-term for CV cause. The RR by quartiles of LVEF was 0.2 (95%CI 0.1-0.3) and 0.5 (95%CI 0.2-1.1), in male and females respectively, for early mortality, p for dis-homogeneity =0.02; and 0.4 (95%CI 0.3-0.6) and 0.6 (95%CI 0.4-0.9), in male and females respectively, for long-term-CV-mortality, p for dis-homogeneity =0.10. Age adjusted gender-LVEF interaction was 2.1 (95%CI 1.1-4.0) p=0.01, for early mortality, and 1.1 (95%CI 0.8-1.5) p=0.55, for long-term-CV-mortality. Full adjusted (age, previous myocardial infarction, NSTEMI, CK-MB peak; β-blockers, ACE-inhibitor/anti angiotensin II receptor blockers, lipid lowering treatment, thrombolysis) early mortality interaction was 2.1 (95%CI 1.1-4.1) p=0.02. Full adjusted long-term-CV-mortality interaction was not significant, p=0.29.
Conclusion: This prospective study showed a gender based different association of LVEF with early mortality after ACS, being women with higher LVEF values at higher risk than men for early mortality.

P5626 | BEDSIDE
G-protein-coupled receptor kinase 5 polymorphism and Takotsubo cardiomyopathy

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Purpose: Takotsubo cardiomyopathy (TTC) is an increasingly reported clinical syndrome that mimics acute myocardial infarction with no obstructive coronary artery disease and transient systolic dysfunction of the apical and/or midsegments of the left ventricle. The syndrome occurs mainly in postmenopausal women with high adrenergic state conditions. Nowadays, the pathophysiology of TTC is not yet known and the possibility of a genetic predisposition is controversial. The aim of this study was to assess the genetic susceptibility to TTC through analysis of the L41Q polymorphism of the G-protein-coupled receptor kinase 5 (GRK5).
Methods and results: In a cohort of 20 patients enrolled in two tertiary centers with diagnosis of TTC, accordingly to the commonly accepted Mayo Clinic criteria, we evaluated the polymorphism in GRK5 gene and compared them with 22 healthy subjects (control). The TTC patients had a mean age of 65±9 years and 19/20 were female. The presence of one or two L41 allels of GRK5 was significantly more frequent in TTC group than in control group (40% vs 8%, p=0.0372).
Conclusions: In our study we found a significant difference in the frequency of GRK5 polymorphism between TTC patients and controls, supporting a genetic predisposition to this cardiac syndrome.

P5627 | BEDSIDE
Body composition and the severity of acute decompensated heart failure

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Background: Heart failure (HF) is a clinical syndrome associated with diverse metabolic disturbances. Recent studies demonstrated that both less body fat (BF) and skeletal muscle mass might be associated with cardiac cachexia and they could predict the future events in chronic HF patients. However, the clinical significance of body composition in patients with acute decompensated HF (ADHF) remains unclear.
Methods: We assessed BF and appendicular skeletal muscle mass by dual energy X-ray absorptiometry in 60 patients with ADHF (age 71±10, 67% male, left ventricular ejection fraction (LVEF) 38±16%, B-type natriuretic peptide (BNP) levels on admission 597 [294-1271] pg/ml). Patients were divided into low or high BF group by the cut-off value of 18% in male and 28% in female (median). Sarcopenia was defined as the appendicular skeletal muscle mass index (ASMI, appendicular skeletal muscle mass/height2) 2 standard deviations below the mean of young healthy Japanese subjects (<6.87 kg/m^2 in male, <5.46 kg/m^2 in female).
Results: Both BF and ASMI significantly correlated with age (r=-0.31, P=0.02 and r=-0.27, P=0.04), male sex (r=-0.46, $P<0.001$ and r=0.49, $P<0.001$), body mass index (r=0.68, $P<0.001$ and r=0.50, $P<0.001$), and BNP levels (r=-0.43, P=0.001 and r=-0.27, P=0.04). BF and ASMI were independent of each other (r=-0.09, P=0.50). ADHF patients with low BF had more severe HF symptoms (New York Heart Association class- 2.8±0.6 versus 2.5±0.5, p=0.05) and higher BNP levels (1013 [581-1773] versus 377 [245-1048], p=0.001) than those with high BF. ADHF patients with sarcopenia (n=31, 52%) had more severe HF symptoms (New York Heart Association class- 2.8±0.5 versus 2.5±0.5, p=0.01), higher BNP levels (913 [457-1405] versus 396 [245-1098], p=0.03), and higher rate of clinical scenario 2-3 (45% versus 17%, p=0.02) than those without sarcopenia. Stepwise backward multivariate logistic regression analysis including age, gender, and LVEF demonstrated that low BF (odds ratio: 9.3, 95%-confidence interval: 2.4-36.0, P=0.001) independently correlated with higher BNP levels (above median) in ADHF patients.
Conclusions: Less body fat and skeletal muscle mass are associated with the severity of ADHF.

DIABETES UNDER SIEGE

5705 | BENCH
Coffee consumption and risk of prediabetes in hypertension: results of the HARVEST study

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Aims: Whether and how coffee use influences glucose metabolism is still a matter for debate. The CYP1A2 polymorphism has been shown to modulate the association of coffee use with cardiovascular outcomes. We investigated whether baseline coffee consumption is associated with risk of prediabetes in a cohort of 18-to-45 year old subjects with stage 1 hypertension and studied the effect of coffee intake on incident prediabetes within subjects stratified by CYP1A2 genotype.
Materials and methods: A total of 1,180 nondiabetic patients attending 17 hospital centers were included. Genotyping of CYP1A2 SNP was performed by real time PCR in 639 subjects. Prediabetes was defined as fasting plasma glucose measured at the final available visit between 100 and 125 mg/dL.
Results: Seventy-four percent of our subjects drank coffee. Among the coffee drinkers, 87% drank 1–3 cups/day (moderate), and 13% drank over 3 cups/day (heavy). CYP1A2 genotype frequencies were: *1A*1A=41.9%, *1A*1F=43.7%, *1F*1F=14.4%. At the end of a median follow-up of 6.1 years, prediabetes was diagnosed in 24.0% of the subjects (27.1% in men and 15.9% in women, $p<0.001$). In a multivariable Cox regression coffee use was a predictor of incident prediabetes ($p<0.001$), with a hazard ratio (HR) of 1.34 (95%CI, 0.99-1.83) in moderate coffee drinkers and of 2.02 (1.31-3.11) in heavy drinkers compared to abstainers. The association of coffee use with incident prediabetes remained significant in the subjects with overweight or obesity (n=586, p=0.002) whereas it lost statistical significance in the subjects with normal weight (p=0.24). Among the subjects stratified by CYP1A2 genotype, heavy coffee drinkers carriers of the slow *1F allele (59%) had a higher adjusted risk of prediabetes (HR, 2.78, 95%CI, 1.32-5.88) than those homozygous for the A allele (HR, 1.71, 95%CI, 0.76-3.84). Urinary epinephrine showed a linear increase with increasing coffee use (p=0.029).
Conclusions: These data show that coffee consumption increases the risk of prediabetes in hypertension particularly among carriers of the slow CYP1A2 *1F allele and in individuals with overweight or obesity.

5706 | BEDSIDE
Association between mind-body practice and cardiometabolic risk factors: the Rotterdam study

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Purpose: In this study we aimed to determine the association between mind-body (MB) practice and cardiometabolic risk factors.
Methods: This study was embedded within the population-based Rotterdam Study (visit 2009-2013) and included 2579 participants free of cardiovascular dis-

ease. Participants were categorised according to their involvement in any form of MB practice (i.e. ≥1 hour per week of meditation, yoga, self-prayer) based on a structured home interview. Cardiometabolic risk factors (body mass index (BMI), blood pressure, and fasting blood levels of cholesterol, triglycerides, and glucose) were individually analysed with linear regression. Presence of the metabolic syndrome (according to the National Cholesterol Education Program (NCEP)) was analyzed with logistic regression. Analyses were adjusted for age, sex, educational level, smoking, alcohol consumption, (in)activities in daily living, grief, and stress.

Results: In our study population (57.5% women, mean age 66.2±7.6 years), 16.6% of the participants were involved in any form of MB practice. Those who were involved in MB practices had significantly lower BMI, total cholesterol levels, triglyceride levels, and glucose levels (Table 1). Additionally, the odds-ratio for the presence of metabolic syndrome was 0.68 (95%CI 0.52;0.90) for individuals performing mind-body practices.

MB practice and cardiometabolic risk

	β*(95% conficence interval)	p-value
Body mass index, kg/m^2	–0.82 (–1.26; –0.38)	<0.001
Systolic blood pressure, mmHg	–1.47 (–3.52; 0.58)	0.160
Diastolic blood pressure, mmHg	–0.77 (–1.93; 0.39)	0.191
Total cholesterol, mg/dL	–4.45 (–8.56; –0.34)	0.034
High-density lipoprotein, mg/dL**	0.001 (–0.01 ;0.01)	0.927
Low-density lipoprotein, mg/dL	–3.32 (–7.17; 0.53)	0.091
Triglyceride, mg/dL**	–0.02 (–0.04; –0.002)	0.032
Fasting glucose, mg/dL**	–0.01 (–0.02; –0.01)	<0.001

*Adjusted for age, sex, educational level, smoking, alcohol consumption, activities of daily living, grief, and stress. **Log transformed.

Conclusions: Persons involved in mind-body practices have a favourable cardiometabolic risk profile compared to those who are not. However, our findings do not indicate a causal relation.

5707 | SPOTLIGHT
Growth differentiation factor-15 predicts diabetic cardiomyopathy in asymptomatic patients with type 2 diabetes

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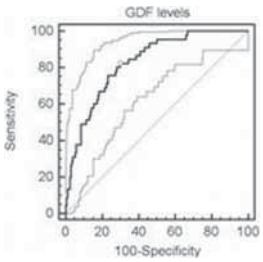
Purpose: Growth differentiation factor-15 (GDF-15) is a stress-responsive cytokine that is increased in established type 2 diabetes (T2D). Diabetic cardiomyopathy (DC) is defined as left ventricular diastolic dysfunction (LVDD) in patients with T2D in the absence of arterial hypertension, ischemic heart disease or other heart disease. We assessed whether GDF-15 can predict diabetic cardiomyopathy (DC).

Methods: We prospectively included 213 consecutive outpatient T2D patients, 65.7% males, aged 61.5±6.34 years. A complete history and clinical examination was performed, including 12-lead electrocardiogram, symptom-limited treadmill exercise and echocardiography. Plasma GDF-15 concentrations were measured with an automated electrochemiluminescent immunoassay at baseline. DC was defined as LVDD in patients with T2D in the absence of arterial hypertension, ischemic heart disease or other heart disease.

Results: The prevalence of DC was 21.1% (45 patients), while 78.9% (168 patients) did not fulfil the criteria. There were no statistical differences in baseline characteristics (age, gender, dyslipidemia and smoking) between both groups. GDF-15 levels were higher in patients with DC compared to those without DC (5273 [4216.4-6955] vs 2812.66 [2122-4147.3] pg/ml, respectively, P<0.001). We assessed predictors of DC, using multivariate regression analysis. GDF-15 (OR 9.63; 95% CI [3.9-24.2], p<0.001) was the unique independent predictor of DC. The results of receiver operating characteristic curve indicated that the GDF-15 point closest to the upper left angle for the prediction of DC was 3812 pg/ml (AUC=0.83; sensitivity=82.2%, specificity=70.3, p<0.0001) (Figure).



ROC analysis of GDF-15 to predict DC.

Conclusions: Our study indicates that GDF-15 levels represent a useful and novel tool to screen DC in patients with 2TD.

5708 | BEDSIDE
Endothelial dysfunction and arterial stiffness are associated with visual impairment in diabetic patients

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Purpose: Diabetic Retinopathy (DR) is a complication of diabetes mellitus leading to deterioration of vision. Endothelial function and arterial stiffness are key players in the pathophysiology of atherosclerotic disease. We investigated the possible association of vascular function with visual acuity in subjects with diabetes mellitus.

Methods: We enrolled 100 consecutive subjects with diabetes mellitus. Patients were divided in those with DR (53 subjects, mean age 68±9) and those with no evidence of DR (NDR) (mean age 66±6). The diagnosis of DR was made by ophthalmoscopy and best-corrected visual acuity (BCVA) was measured in both eyes. A BCVA less than 0.8 was considered as severely impaired. Endothelial function was evaluated by flow mediated dilation (FMD) in the brachial artery and arterial stiffness was evaluated by carotid femoral pulse wave velocity (PWV).

Results: Although there were no significant differences in baseline characteristics, patients with DR compared to NDR patients had impaired FMD (3.42±1.08% vs. 5.39±1.47%, p<0.001), impaired PWV (11.10±3.11m/sec vs. 9.02±2.13m/sec, p=0.001) and worse BCVA (p<0.001). Moreover in diabetes mellitus subjects, BCVA was positively correlated with FMD, creatinine clearance, and inversely correlated with PWV, glycosylated hemoglobin levels, C- reactive protein levels, age and with duration of diabetes mellitus (p<0.01 for all). Interestingly, after adjustment for age, gender, smoking habits and the aforementioned confounders, FMD was independently associated with BCVA (p<0.001). Moreover, ROC curve analysis revealed that both impaired FMD (AUC=0.79, p<0.001) and PWV (AUC=0.8, p<0.001) have a significant diagnostic ability in detecting diabetic subjects with severely impaired BCVA. More precisely, FMD less than 4.5% has a sensitivity of 90% and a specificity of 60%, while PWV over 10.0 m/sec has a sensitivity of 83% and a specificity of 68%, for the diagnosis of severely impaired BCVA.

Conclusion: Patients with DR have significantly impaired vascular function and visual acuity. Moreover, both endothelial function and arterial stiffness were high sensitivity predictors of visual impairment highlighting their potential role on the prevention and management of the complications in diabetes mellitus.

5709 | BEDSIDE
Global longitudinal strain by speckle-tracking echocardiography is impaired in type 1 diabetes patients with albuminuria – the Thousand&1 Study

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Purpose: Heart failure is a common cause of mortality in Type 1 Diabetes (T1DM). A specific diabetic cardiomyopathy related to kidney disease has been proposed. We hypothesized that speckle-tracking echocardiography could detect changes in left ventricular function associated with albuminuria not measurable by conventional echocardiography.

Methods: Cross-sectional study of 1065 T1DM patients without known heart disease randomly selected from an out-patient clinic. Conventional echocardiography and global longitudinal strain (GLS) by 2D-speckle-tracking echocardiography was performed and analyzed in relation to normoalbuminuria (n=739), microalbuminuria (n=223), and macroalbuminuria (n=103). Investigators were blinded to degree of albuminuria.

Results: Mean age 49.5 years, 52% men, mean HbA1c 8.2% (66 mmol/mol), mean BMI 25.5 kg/m^2, and mean diabetes duration 26.1 years. Left ventricular ejection fraction (LVEF) was not related to albuminuria status (p=0.68). In contrast, GLS differed significantly between degrees of albuminuria, (mean (SE)) -18.5% (0.1) in normoalbuminuria, -17.9% (0.2) in microalbuminuria, and -17.4% (0.3) in macroalbuminuria, all p<0.001. In a multivariable model including significant predictors (age, sex, HbA1c, diastolic blood pressure, BMI, and LVEF),

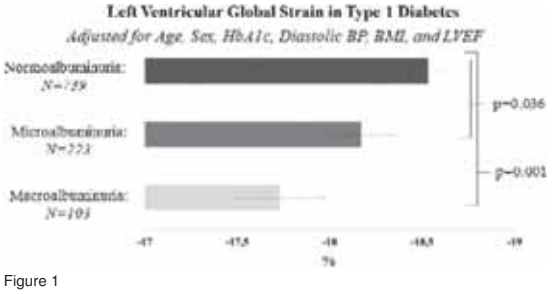

Figure 1

GLS remained different with microalbuminuria (p=0.036), and macroalbuminuria (p=0.001) compared to normoalbuminuria. Including duration of diabetes or reno- and cardioprotective medication did not change the association.
Conclusions: Systolic function assessed by GLS was impaired in T1DM patients with albuminuria and no known heart disease independently of LVEF and other clinical characteristics. These findings suggest early systolic impairment in T1DM and support the concept of a specific diabetic cardiomyopathy.

5710 | BEDSIDE
Impact of pioglitazone on cardiovascular events in patients with diabetes mellitus after drug-eluting stent implantation

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Background: Patients with diabetes mellitus (DM) after drug-eluting stent (DES) implantation is worse clinical outcomes than that of patients without DM. It was reported that Pioglitazone (Pio) decreased cardio-vascular events via its anti-atherosclerotic effects, as well as a blood glucose-lowering effect in patients with DM.
Objective: This study aimed to evaluate the preventive effect of Pio on cardiovascular events in patients with DM after DES implantation based on 1-year follow-up results of the J-DESsERT trial.
Methods: In the J-DESsERT trial, a prospective multicenter randomized controlled trial, 3533 patients with coronary artery disease were randomized 1:1 to coronary stenting with either a sirolimus-eluting stent or a paclitaxel-eluting stent, and followed for 1 year. The criteria of lesion length was $<$46 mm with vessel diameters from $\geq$2.5 to $<$3.75 mm. Definitions for DM in this trial were (1) previous diagnosis of DM; (2) currently on diabetic medication (oral hypoglycemic drugs or injection of insulin preparation); and (3) HbA1c$\geq$6.9% within 30 days before the procedure.
Results: A total of 1705 (48%) participants were diagnosed as having DM. The rate of cardiovascular events (death/myocardial infarction/target vessel revascularization/cerebrovascular disorders) 1 year after DES implantation in patients with DM was significantly higher (11.0%) than that in patients without DM (7.7%) (P$<$0.01). Of the patients with DM, 357 patients (21%) had been medicated with Pio before percutaneous intervention. In patients with DM, the rate of cardiovascular events 1 year after DES implantation in the Pio-treated group was significantly lower (6.7%) than that with other therapies in the group without Pio (12.4%) (P$<$0.01). The rate of target vessel revascularization in the Pio-treated group was significantly lower (4.5%) than that with other therapies in the group without Pio (8.2%) (P=0.02). Multivariate analysis showed that treatment with Pio was associated with the prevention of cardiovascular events in patients with DM (OR=0.55, P=0.01).
Conclusion: Pioglitazone significantly decreased cardiovascular events of patients with DM 1 year after DES implantation. These results suggest that Pio may have a preventive effect on restenosis after DES implantation.

5711 | BEDSIDE
Efficacy of aspirin in people with diabetes: an individual participant data meta-analysis of 26 randomised trials

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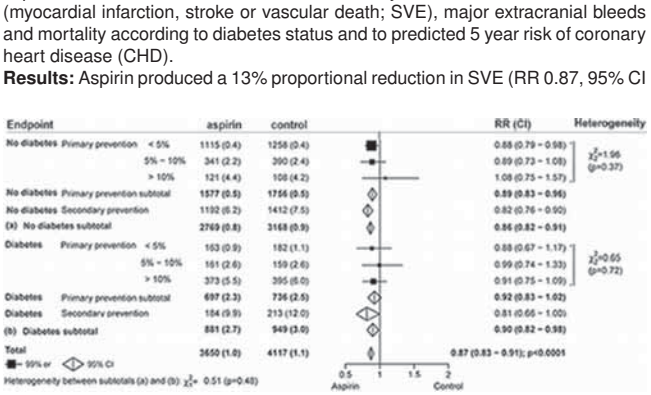
Purpose: It is not known if the efficacy of aspirin is modified by diabetes, or whether aspirin is of net benefit for primary prevention in people with diabetes.
Methods: Individual participant data were available from 26 randomised trials of aspirin versus control. We undertook meta-analyses of serious vascular events (myocardial infarction, stroke or vascular death; SVE), major extracranial bleeds and mortality according to diabetes status and to predicted 5 year risk of coronary heart disease (CHD).
Results: Aspirin produced a 13% proportional reduction in SVE (RR 0.87, 95% CI 0.83-0.91; figure), a 56% proportional increase in major extracranial bleeding (RR 1.56, 95% CI 1.33-1.82) and a 7% proportional reduction in total mortality (RR 0.93, 95% CI 0.89-0.98). These effects were similar irrespective of the presence of diabetes (p=0.39, p=0.32 & p=0.82 respectively). Among people with diabetes there was a 10% proportional reduction in SVE (RR 0.90, 95% CI 0.82-0.98), and no evidence that this reduction differed in primary and secondary prevention (p=0.25). Among people with diabetes in primary prevention, the independent proportional reduction in SVE was not statistically significant (RR 0.92, 95% CI 0.83-1.02): there was no evidence that the proportional effects on serious vascular events differed among people with diabetes at low ($<$5%), medium (5-10%) and high ($>$10%) 5-year risk of CHD (p=0.72), but these analyses lacked statistical power.
Conclusions: The proportional effects of aspirin on SVE, major extracranial bleeding and mortality are similar among people with and without diabetes. Further information about the balance of benefit and hazard of aspirin for primary prevention among people with diabetes, and its relationship to estimated CHD risk, is needed from ongoing trials.



5712 | BEDSIDE
Relationship between diabetes management and coronary atherosclerotic change in non-culprit lesions after percutaneous coronary intervention - Serial integrated backscatter IVUS study -

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Purpose: Diabetic patients continue to have high cardiovascular events after percutaneous coronary intervention (PCI). However, serial changes in volume and tissue characteristics of coronary atherosclerotic plaques in non-culprit lesions after PCI have not been fully investigated. The aim of this study was to investigate the relationship between diabetic management and coronary atherosclerotic plaque changes in non-culprit lesions using IVUS and integrated backscatter IVUS (IB-IVUS).
Methods: We investigated 40 patients with diabetes mellitus (DM) (41 lesions; DM) and 48 patients without DM (50 lesions; non-DM). Volumetric IVUS analyses were performed at proximal non-culprit 5mm lesions in de novo target vessels post PCI and at 6-12 months follow-up. All patients were managed with standard medical treatment during follow-up. We measured serial changes in coronary atherosclerotic plaque burden and plaque composition using IVUS and IB-IVUS in both groups.
Results: Baseline patient characteristics showed that the ratio of hypertension in DM were significantly higher than those in non-DM (p$<$0.005). Otherwise, there was no significant difference between groups. DM demonstrated a greater plaque volume at baseline (DM: 40 mm^3 vs. non-DM: 33 mm^3, p$<$0.01) and follow-up (DM: 43 mm^3 vs. non-DM: 32 mm^3, p$<$0.0001) than non-DM. Plaque volume change also showed significant difference between groups (DM: + 2.2 mm^3 vs. non-DM: - 1.2 mm^3, p$<$0.04). DM were further divided into 2 groups according to follow-up glycated hemoglobin A1c (HbA1c) levels of $\geq$7.0% (20 patients with 20 lesions) and $<$7.0% (20 patients with 21 lesions). Plaque volume change was significantly larger in HbA1c $\geq$7.0% than that in HbA1c $<$7.0% (+ 4.6 mm^3 in HbA1c $\geq$7.0%, - 0.1 mm^3 in HbA1c $<$7.0%, p$<$0.05). There was no significant difference in change in lipid plaque volume between DM and non-DM. However, change in lipid plaque volume significantly correlated with change in LDL-cholesterol level in DM (Y = 0.07X + 2.1, r=0.32, p$<$0.05), whereas it did not in non-DM (p=0.14).
Conclusions: In diabetic patients, coronary atherosclerotic plaque progression was induced by poor glycemic control and high LDL-cholesterol level under standard medical treatment. Intensive medical treatment should be required to control non-culprit coronary plaque progression.

5713 | BEDSIDE
Incidence and impact of hypoglycemia in diabetic patients with intensified glycaemic control in clinical practice - results of DiaRegis

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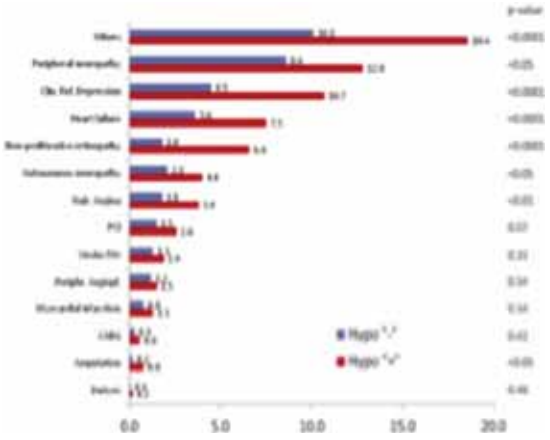
Background: Randomized trials showed, that intensified treatment of type 2 diabetes (T2D) led to higher rates of hypoglycaemia (hypo). Little is known about on the incidence and the prognostic impact of hypo in clinical practice.
Methods: DiaRegis is a prospective, observational, multi-centre registry with a 2 year follow-up in patients with T2D in whom anti-diabetic treatment was intensified due to prior insufficient glucose control. We examined the incidence and and impact of hypo in clinical practice
Results: Out of 3,058 patients, 75 (2.5%) died, the incidence of hypo was 17.8% with a mean of 5.4$\pm$5.8 episodes per patient, and was independent from glucose control (HbA1c, fasting / postprandial plasma glucose). Predictors of hypo were heart failure (OR 1.66; 95%CI 1.20-2.29) and insulin therapy (OR 4.03; 95%CI 3.05-5.33). Predictors of symptomatic hypo requiring help were age$>$65

years (OR 2.09; 95%CI 1.10-3.98), male gender (OR 1.99; 95%CI 1.09-3.64), heart failure (OR 2.40; 95%CI 2.07-16.70) and history of prior hypo (OR 5.88; 95%CI 2.07-16.70). The use of DPP-4 inhibitors was associated with a 31% relative risk reduction for hypo (OR 0.69; 95%CI 0.53-0.89). Macro-vascular events (new MI, stroke and PAD) were more frequent in patients with severe hypo (OR 3.39 for macro-vascular events, 5.28 for new MI). Micro-vascular events (not previously known retinopathy, nephropathy, neuropathy, and amputation) were more frequent in those with non-severe hypo (OR 1.92; 95%CI 1.49-2.49).



Complications dependent on hypoglycemia.

Conclusions: Hypo is frequent in intensified glucose control of T2D. It is associated with an increased micro- and macro-vascular complications. Considering individual patient characteristics and co-morbidity, careful selection of anti-diabetic pharmacotherapy have the potential to avoid complicating hypo.

5714 | BEDSIDE
Diabetes mellitus may not be a risk of stroke in Japanese patients with atrial fibrillation: From the Fushimi AF Registry

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Purpose: Atrial fibrillation (AF) is a common arrhythmic disorder among the elderly, and is increasing significantly as the population ages (reportedly 0.6% of total population in Japan). Diabetes mellitus (DM) is considered a major risk factor of ischemic stroke in patients with atrial fibrillation (AF), and is one of the components of CHADS2 score. The purpose of this study was to investigate the relationship between DM and incidence of stroke in Japanese AF patients.
Methods: The Fushimi AF Registry, a community-based prospective survey, was designed to enroll all of the AF patients in Fushimi-ku, Kyoto. Fushimi-ku is densely populated with a total population of 283,000, and is assumed to represent a typical urban community in Japan. At present, we have enrolled 3,821 patients (1.4% of total population) from March 2011 to December 2013. One-year follow-up was completed in 2,966 patients as of December 2013.
Results: 698 patients were diagnosed as DM (23.5% of total, the mean age 73.7 years) and 2,268 patients were without DM (76.5% of total, the mean age 73.9 years). DM patients, compared with non-DM patients, had more co-morbidities (hypertension, dyslipidemia, coronary artery disease, and chronic kidney disease), and thus had higher CHADS2 score (DM vs. non-DM: 2.98 vs. 1.77; $p<0.0001$). They received more anticoagulation prescription (57.6% vs. 51.4%; p=0.0040), but the rate of previous stroke was comparable (20.1% vs. 19.1%; p=0.57).
During one-year follow-up period, the incidence of bleeding, hospitalization for heart failure and all-cause death were not different between two groups (bleeding: 5.16% vs. 3.97%; p=0.18, heart failure: 4.87% vs. 3.84%; p=0.24, death: 8.17% vs. 8.07%; p=0.93).
The incidence of stroke was also equivalent (3.01% vs. 2.43%, p=0.40). This was also the case when we divided the entire cohort into patients under oral anticoagulants and those without them (with anticoagulants 2.49% vs. 2.58%, p=0.92; without 3.72% vs. 2.27%, p=0.18).
Furthermore, Multiple logistic regression analysis including risk factors of CHADS2 score and anticoagulation prescription revealed that the age and previous stroke were independent determinants of stroke, but DM was not an independent determinant of stroke [odds ratio: 1.21, 95% confidence interval: 0.71-2.01, p=0.47].
Conclusion: The Fushimi AF registry represents the clinical profile of real-world Japanese AF patients. DM may not be a risk of stroke, at least in Japanese AF patients.

UPDATES ON ENDOCARDITIS AND ON TRICUSPID REGURGITATION

5715 | BEDSIDE
Temporal trends in infective endocarditis. Insights from a multicenter 1100-patient cohort study

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Aim: To evaluate epidemiological and microbiological changes in infective endocarditis (IE) in the last two decades, and to assess the impact of these changes on patients' outcome.
Methods: We analyzed 1120 consecutive episodes of IE who were recruited prospectively at 3 referral centers between 1996 and 2012. They were classified into 2 groups: Group I (N=497), episodes of IE from 1996 to 2004, and Group II (N=623), episodes from 2005 to 2012.
Results: Patients from Group II were older (59 (±16) vs 65 (±14); $p<0.001$). The frequency of patients with comorbidities, including diabetes (15.7% vs 23.4%; p=0.001), malignancies (6.9% vs 12.7%; p=0.001), chronic renal insufficiency (8.1% vs 15.2%; $p<0.001$), and history of intravenous drug use (11% vs 2.4%; $p<0.001$) increased significantly during the study period. Nosocomial episodes of IE were more frequent (29.3%% vs 34.4%; p=0.005) in the last period. Degenerative valvulopathy (8.7% vs 16.7%; $p<0.001$) was also more frequent in this group. Enterococcus infection significantly increased over time (6.5% vs 10.1%; p=0.039). S.aureus remained the most common cause of IE in both periods of time (19% of cases). Vegetation detection was more common in Group II (79.2% vs 86%; p=0.004). Periannular complications were similar in both groups. Clinical events during hospitalization appeared more frequently in the second period (Table). However, the percentage of patients that underwent surgery and in-hospital mortality rate were similar in both groups.

In-hospital evolution

	Group I: 1996–2004	Group II: 2005–2012	P value
Central nervous system embolisms	25 (5.2%)	86 (14.0%)	<0.001
Acute renal insufficiency	222 (45.8%)	328 (53.8%)	0.009
Heart failure	271 (55.9%)	376 (61.6%)	0.050
Cardiac surgery	267 (53.9%)	360 (58.3%)	0.145
In-hospital mortality	148 (29.9%)	165 (28.6%)	0.686

Conclusions: Epidemiologic and microbiologic profile has changed in the last two decades. Patients from the last period were older, had more comorbidity and a more virulent microbiological profile than those from the first period. As a result, the incidence of in-hospital events was higher in this group. Nevertheless, in-hospital mortality did not change over the study period.

5716 | BEDSIDE
Added value of 18F-FDG PET/CT-Angiography with myocardial suppression in the diagnosis of infective endocarditis in prosthetic valves and intracardiac devices

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Purpose: To evaluate the added value of 18F-FDG PET/CT-Angiography (PET/CTA) in the diagnosis of infective endocarditis (IE) in prosthetic valves (PV) and cardiac devices (CD), where modified Duke criteria (DC) and echocardiography (ECHO) have limitations.
Methods: A prospective study was conducted in a hospital with a multidisciplinary IE unit. PET/CTA was performed and compared with ECHO in all consecutive patients with suspected prosthetic IE, with exclusion of unstable patients requiring emergent surgery. Initial diagnosis with DC, PET/CTA and DC+PET/CTA information were compared with a final expert team diagnostic consensus performed with all clinical, microbiological and imaging information.
Results: 39 patients (32 men; median age 64 years) from Nov-12 to Feb-14 entered the study. Patients had PV aortic tubes: 6; PV: 13; CD: 10; PV+CD: 6 and prosthesis in congenital corrections: 4. ECHO was positive in 15, negative in 16 and doubtful in 8 cases. PET/CTA was positive in 24, negative in 14 and doubtful in 1 case. PET/CTA and ECO were concordant in 59% (kappa:0.3) and among discordant cases, PET/CTA confirmed and accelerated the diagnosis of IE in 9 false negative/doubtful ECHO and ruled out IE in 4 false positive/doubtful ECHO. In patients who had a PV+CD, PET/CTA could locate the site of infection in all cases.
Table shows IE classification. DC+PET/CTA allowed reclassification of 59% of the IE initially classified as (P) confirming/ruling out diagnosis, and the expert team could give a more conclusive diagnosis (D/R) in 73% of (P) IE. Sensibility, specificity, PPV and NPV were 48.1%/100%/100%/79.1% for DC, 81.5%/83.3%/91.7%/66.7% for PET/CTA and 85.2%/83.3%/92%/71.4% for DC+PET/CTA. PET/CTA additionally provided an alternative diagnosis in 55% of

EI classification	Duke criteria	PET/CTA	DC + PET/CTA	Expert team consensus
Definitive (D)	13 (33%)	24 (62%)	25 (64%)	24 (62%)
Possible (P)	17 (44%)	1 (2.6%)	7 (18%)	4 (10%)
Rejected (R)	9 (23%)	14 (36%)	7 (18%)	11 (28%)

the (R) IE, detected peripheral embolisms in 10 cases and 4 unsuspected neoplastic lesions.
Conclusions: PET/CTA could be a useful diagnostic tool in the diagnosis of prosthetic IE with an added diagnostic value to modified DC, increasing its sensibility, and allowing the expert team final consensus a more definitive classification.

5717 | BEDSIDE
Respective performances of FDG-PET and radiolabeled leukocyte scintigraphy for the diagnostic of prosthetic valve endocarditis

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Purpose: Echocardiography plays a key role in the infective endocarditis (IE) diagnosis but can be inconclusive in patients with suspicion of prosthetic valve (PVE)-IE. The incremental diagnostic value of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) and radiolabeled leukocyte scintigraphy (LS) has already been demonstrated in IE patients. The aim of this study was to compare the respective performances of FDG-PET and LS for the diagnosis of PVE in 39 patients.
Methods: FDG-PET and LS were performed in 39 patients admitted for a clinical suspicion of PVE and inconclusive echocardiography. All patients underwent both FDG-PET and LS, which were analysed separately and retrospectively by experienced physicians blinded to the results of the other imaging technique and to patient's outcome. Final Duke-Li IE classification was performed after a 3-month follow-up period.
Results: Mean age and sex ratio were respectively 62±17 years and 56%. Patients were imaged on average 45 months (range: 14 days - 24 years) following cardiac surgery. Average time interval between FDG-PET and LS acquisitions was 7±7 days. Out of the 39 patients, 15 patients were classified with definite IE, 3 possible IE and 21 excluded IE. Sensitivity, specificity, positive predictive value and negative predictive value were 93%, 71%, 70% and 94% for FDG-PET and 60%, 100%, 100%, and 78% for LS, respectively. Discrepancies between the results of FDG-PET and LS occurred in 12 patients (31%). In patients with definite IE, 5 were identified with true positive FDG-PET but false negative LS. Out of these 5 patients, 3 presented non-pyogenic microorganism IE (Coxiella or Candida). In patients with excluded endocarditis, 6 patients were identified with true negative LS but false positive FDG-PET. These 6 patients had been imaged in the first two months following the last cardiac surgery. The last patient with a discrepancy between FDG-PET and LS was classified as a possible endocarditis and presented positive FDG-PET and negative LS.
Conclusions: FDG-PET offers a high sensitivity for the detection of active infection in patients with a suspicion of PVE and inconclusive echocardiography. LS offers however a higher specificity than FDG-PET for IE diagnosis and should be considered in case of inconclusive FDG-PET findings or in the first two months after cardiac surgery.

5718 | BEDSIDE
High mortality associated with sepsis or endocarditis after pacemaker and ICD implantation - a nationwide cohort study

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Purpose: To determine the cumulative incidence, predictors and risk of mortality after sepsis and overall infective endocarditis (IE) among first-time cardiac implantable electronic device recipients in Denmark.
Methods: We identified all de novo pacemakers (PMs) and implantable cardioverter defibrillators, (ICDs) in the period 1997-2012 from nationwide administrative registers. Logistics and Cox regression models were used to determine significant predictors for sepsis and IE and their associated mortality.
Results: A total of 45,590 first-time PM/ICD recipients (mean age 73 (SD 14) years, 59.5% males) were identified. PMs (N=37,903 (83%)) and dual/multi chamber PMs/ICDs (as opposed to single) (N=26,759 (58.7%)) constituted the largest part of the implantations. In the entire cohort 643 (1.4%) and 296 (0.7%) had a history of sepsis and IE, respectively. Prevalent comorbidities were heart failure (53.9%), ischemic heart disease (31.1%), atrial fibrillation/flutter (27.6%) and conditions requiring treatment with oral anticoagulants (OAC) (25.5%). Mean follow-up duration was 4.8 (SD 3.7) years with an estimated cumulative sepsis and IE incidence of 6.1% (n=2,777) and 1.3% (n=612), respectively. Important predictors for sepsis were age (odds ratio [OR], 1.05; 95% confidence interval [CI], 1.03-1.07), male gender ([OR], 1.36; 95% [CI], 1.25-1.48), previous sepsis ([OR], 2.59; 95% [CI], 2.08-3.22) and OAC ([OR], 1.12; 95% [CI], 1.02-1.22). Important predictors for IE were male gender ([OR], 1.61; 95% [CI], 1.35-1.95), previous IE ([OR], 9.02; 95% [CI], 6.43-12.65), OAC ([OR], 1.43; 95% [CI], 1.19-1.71)and dual/multi chamber PM/ICD ([OR], 1.50; 95% [CI], 1.23-1.83), while aging had a protective effect ([OR], 0.89; 95% [CI], 0.87-0.91). Overall long-term mortality was 21,101 (46.3%) with a significantly higher risk after sepsis (N=2,088 (75.2%), hazard ratio [HR], 4.11; 95% [CI] 2.08-6.05) and IE (N=312 (51.0%), [HR], 2.10; 95% [CI] 1.50-4.35), respectively.
Conclusion: Approximately seven percent of first-time PM/ICD recipients developed subsequently sepsis or IE with both conditions being associated with a high mortality risk.

5719 | BEDSIDE
Impact of an infective endocarditis multidisciplinary team on mortality in a tertiary university hospital

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Background and purpose: Mortality from infectious endocarditis (IE) remains very high. Standardized team approach has been proposed to increase early diagnosis and improve management in IE. We sought to determine the impact of the creation of a IE multidisciplinary team (IEMT) in a tertiary university hospital.
Methods: A retrospective observational study was conducted in a tertiary university hospital. All IE patients admitted from Sept 2008 to Dic 2013 were divided in 2 groups according to the date of the creation of an IEMT (January 2011). Period 1 (P1): Sept 2008- Dic 2010 and Period 2 (P2): Jan 2011- Dic 2013. The IEMT included cardiologists, cardiovascular surgeons, microbiologists, infection specialist and anesthetists.
Results: 95 IE patients (66% male; mean age: 64±15years) were admitted during the study period, 38 in P1 and 57 in P2. 80% of IE involved the mitral or aortic valve. 42 cases (44%) were prosthetic valve IE (37% early endocarditis). 48% of the patients had embolic events and 27% intracardiac complications. Patient's characteristics did not differ between both periods.
The mortality rate was lower in P2 than in P1 (25.5% vs 47.4%; p=0.027). Mean time to diagnosis was also lower (7±12 vs 20±34 days, p=0.027). During P2 more patients underwent cardiac surgery (53% vs 34%, p=0.07), and time from diagnosis to surgery was lower (8±9 vs 15±16 days, p=0.08). However, time to surgery was not related with mortality. On univariate analysis 5 factors were associated with mortality: period 1 (OR: 2.63, p=0.027), coagulase-negative IE (OR: 3.4, p=0.05), absence of cardiac surgery when indicated (OR: 5.2, p=0.019), persistent bacteriemia (OR: 14, p=0.003), and patient in not under direct care by a cardiologist (OR: 31, p=0.000).
Conclusions: Our data support that a MT approach lead by a cardiologist is the most appropriate model of organization to treat and reduce mortality in patients with IE.

5720 | BEDSIDE
Prevalence and echocardiographic correlations of tricuspid regurgitation in patients with significant left ventricular dysfunction

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Purpose: To evaluate for prevalence and clinical significance of tricuspid regurgitation (TR) in patients with left ventricular (LV) dysfunction.
Methods: A single center analysis for TR of all echocardiographic studies, performed between 2000 and 2013 in patients with ejection fraction<35% was performed. Patients with mechanical valves, mitral stenosis, moderate to severe aortic stenosis or regurgitation, were excluded. Associations of TR with baseline echocardiographic findings and mortality were performed using Chi–square test.
Results: The study included 4028 patients (25% female, age 69±2.5 years). Seventy percent had no or mild TR, 23.7% had moderate and 6.3% had severe TR. Females had significantly more TR than males 8.1% vs. 5.7% had severe, 25.8% vs. 22.9% had moderate and 33.4% vs. 32.8% had mild TR; (p<0.001). LV dimensions were not associated with TR severity, however, severity of TR significantly correlated with mitral regurgitation (r=0.448, p<0.001) irrespective of left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), age, gender or body mass index. Left atrial diameter and left atrial area associated with TR severity as well (P<0.001). Severity of TR was significantly (p<0.001) associated with pulmonary hypertension assessed by gradient over the tricuspid valve. Total mortality during follow-up was 63.6%. There was a significant association between TR grade and mortality (58% in no or mild TR, 73% in moderate and 82% mortality in patients with severe TR; p<0.001).
Conclusion: Significant TR occurs frequently (30%) in patients with LV dysfunction and has prognostic implications. Female gender, MR, LA size and pul-

monary hypertension correlate with TR severity and may have possible mechanistic and/or prognostic implications.

5721 | BEDSIDE
Right ventricular dysfunction but not tricuspid regurgitation is associated with outcome in patients after left-sided valve surgery

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Background: Significant tricuspid regurgitation (TR) after previous left-heart valve surgery is frequent and associated with increased morbidity. Mortality rates for re-operation are high, while the impact of TR on survival in these patients remains unclear.
Methods: 571 consecutive patients 49±29 months after left heart valve surgery were prospectively followed for 53±15 months. Significant TR was defined as TR ≥ moderate by echocardiography.
Results: Significant TR was present in 123 (21.5%) patients (64% female, p=0.002). Patients with significant TR more often had atrial fibrillation (46% vs. 20%, p<0.001), they were more symptomatic (NYHA≥II 56% vs. 31%, p<0.001), presented with larger right ventricles (RV; 37.5±7.0mm vs. 33.1±4.7mm, p<0.001), larger left and right atria (66.8±12.5mm vs. 57.7±7.8mm and 64.9±12.4mm vs. 55.6±7.3mm; both p<0.001), lower glomerular filtration rates (61±17 vs. 68±18 ml/min), worse left ventricular (LVEF<50%: 19% vs. 11%; p=0.032) and RV systolic function (17% vs. 3%, p<0.001). 127 (22.2%) patients died during follow-up: 84 patients with significant TR vs. 43 without (p<0.001). By Kaplan-Meier analysis, overall survival was worse in patients with significant TR (log rank p<0.001). However, by multivariable Cox analysis, age (p<0.001), left atrial size (p<0.001) coronary artery disease (p=0.011), chronic obstructive pulmonary disease (p=0.047) and RV dysfunction (p=0.032) but not TR were significantly associated with mortality.
Conclusion: RV dysfunction but not TR late after left-sided valve surgery is significantly associated with survival. Thus isolated surgery of TR in this setting has to be scrutinized. Further studies are needed to define specific patient groups that would clearly benefit from such a procedure.

5722 | BEDSIDE
Long-term outcomes of surgery for severe tricuspid regurgitation in patients who underwent previous open heart surgery

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Purpose: Patients with severe tricuspid regurgitation who need surgical treatment usually have any left valve disease or any congenital heart disease that previously required surgical treatment. Our aim was to analyze clinical outcomes of surgery for severe tricuspid regurgitation in patients who underwent previous heart surgery.
Methods: In this retrospective study, we included all patients with severe tricuspid regurgitation who underwent surgery for tricuspid valve replacement or repair in our center between April 1996 and November 2012 and in addition to this had underdone previous open heart surgery. We analyzed perioperative and long-term mortality, and we indentified predictive factors using multivariable analysis.
Results: 190 patients underwent surgery for severe tricuspid regurgitation, and 33.1% of them (63 patients) had undergone previous heart surgery. These 63 patients were included in this study. 83.7% of the patients were female. Mean age was 60.1±10.7 years, and mean logistic EuroSCORE was 15±7.3. Table shows data regarding previous heart surgery. Concerning the surgery for tricuspid regurgitation, ringless annuloplasty was performed in 23.8% of the patients, ring annuloplasty in 25.4%, 28.6% of patients received a bioprosthesis and 22.2% a mechanical prosthesis. Only 33.3% of these interventions exclusively involved the tricuspid valve, 22.2% involved implanting an aortic prosthesis, 50.8% implanting a mitral prosthesis, 1.6% implanting a pulmonary prosthesis, and 3.2% involved mitral repair. Perioperative mortality was 19%, and it was related to age (OR 1.1 1.02-1.2 p 0.02) and to tricuspid mechanical prosthesis (OR 10.2 1.8-55.7 p 0.07). After a follow-up (median 62 months) conducted in 100% of patients, mortality was 39.7%, and it was related to age (HR 1.6 0.01-1.11 p 0.009) and to extracorporeal circulation time (HR 1.01 1.005-1.018 p 0.001).

Previous heart surgery	
Mitral valve replacement or repair	81% of patients
Aortic valve replacement	22% of patients
Correction of congenital heart defects	7.9% of patients

Conclusions: Surgery for severe tricuspid regurgitation in patients who underwent previous heart surgery showed a high mortality. Age and tricuspid mechanical prosthesis were predictors of perioperative mortality. Age and extracorporeal circulation time were predictors of long-term mortality.

5723 | BEDSIDE
Functional tricuspid regurgitation in organic mitral regurgitation. New insights in right ventricular function

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Objective: To assess the determinants of functional tricuspid regurgitation (TR) and its relations to right ventricular (RV) function in chronic organic mitral regurgitation (MR).
Methods: Three-hundred twenty-five patients (63±12 years, 206 males) with organic MR (82% degenerative etiology) referred to surgery and who underwent a preoperative gradation of TR were included in this study. Radionuclide angiography was carried out in 237 patients.
Results: Fifty patients had a TR ≥ grade 2. Patients with TR ≥2 were older, had more AF (54 vs 24%, P<0.0001) and were more symptomatic. Mean LV EF and RV EF were lower, and LV septal function and RV free wall function were impaired in those with TR ≥2. By echocardiography, LV-RV, left and right atrial remodeling were worse, PASP was higher and inter ventricular systolic pressure was lower whereas the severity of MR was similar. RV S velocity was also significantly decreased. Ventricular function was stratified in normal RV-LV (Normal), isolated RV dysfunction (RVdysf, RV EF≤35%), isolated LV dysfunction (LVdysf, LV EF<60%), and biventricular impairment (BiV, LV EF<60% and RV EF≤35%). TR ≥2 was found mainly in either BiV (33%) or LVdysf (22%) but almost never in RVdysf (3%) nor Normal (3%) groups. In BiV TR ≥2 was associated with overall impairment of the right heart while only the RA-annulus-RV base were enlarged in LVdysf. Finally RV EF alteration in RVdysf was likely linked mainly to compression and flattening of the RV by the severely enlarged LV owing to severe volume overload. Moreover, in RVdysf volume overload was higher, RV S wave velocity was not reduced, and RV EF improvement after surgery was greater suggesting limited impairment of intrinsic myocardial function. These specific features probably explain the absence of TR in this subgroup of patients.
Conclusions: In patients with organic MR referred to surgery TR ≥2 is associated with the longstanding consequences of chronic organic MR. Significant TR occurs mainly in patients with BiV or LVdysf but is almost absent in RVdysf or Normal groups. Finally RVdysf group exhibits features suggesting a direct reversible effect of volume overload on the RV.

5724 | BEDSIDE
Caval Valve Implantation (CAVI) as interventional treatment option for severe Tricuspid Regurgitation - summary of current preclinical and clinical evidence

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Objective: Transcatheter caval valve implantation (CAVI) is a novel treatment option for inoperable patients with severe tricuspid regurgitation (TR). The procedure involves the catheter-based deployment of bioprosthetic valves in the inferior (IVC) and superior (SVC) vena cava to treat venous congestion and symptoms of right heart failure. While our institution uses custom-made, self-expandable devices sized to the individual patient, others following this concept have used commercially available, ballon-expandable devices. Herein, we summarize the up-to-date experience with this treatment approach from basic preclinical studies to current human application.
Methods and results: Acute and chronic proof-of-concept studies were performed in a sheep model of severe TR. Following the induction of TR, two self-expanding valves were implanted into the SVC and IVC in these animals resulting in a significant decrease of the ventricular wave ("v"-wave) from 16.2±2.33 mmHg to 13.9±2.97 mmHg and a significant increase of cardiac output from 2.9±1.16 l/min to 4.20±0.84 l/min. Valve function was documented in this model up to 6 month after implantation. Autopsy results verified correct device position and valve function in all successfully implanted animals.
Based on this encouraging preclinical experience, the concept was applied for compassionate treatment in four inoperable patients (78±4.6 years, female: 100%) with severe TR. In these patients, either one or two self-expanding pericardial tissue valves were implanted in the IVC alone (n=2) and or in both caval veins (n=2). After deployment, transesophageal echo confirmed excellent function in all implanted devices. Hemodynamic measurements confirmed a nearly abolished "v"-wave in the IVC from 30.0±3.4 to 19.3±2.9 mmHg, mean IVC pressure decreased from 20±2.2 to 16±2.4 mmHg.
In-hospital mortality was 50%. In patients discharged from Hospital symptoms of RV failure resolved and did not recurr during a follow-up period of 3 and 11 month. In one patient, synthetic liver function recovered and the distance covered in 6-minute-walk-test increased from 20m before implantation to 360m at 11 month.
Conclusion: Transcatheter caval valve implantation for treatment of severe TR is feasible resulting in an immediate abolition of caval regurgitation and midterm clinical improvement. In selected non-surgical patients, CAVI can be considered as therapeutic option to treat venous regurgitation and improve hepatic congestion. Further confirmatory experience with longer follow-up is required to evaluate the long-term clinical benefit of the procedure.

LIPID SIGNALLING AND INFLAMMATION

5738 | BENCH
ApoA-I mimetic peptide FAMP induces neovascularization through activation of endothelial cell nitric oxide related pathway

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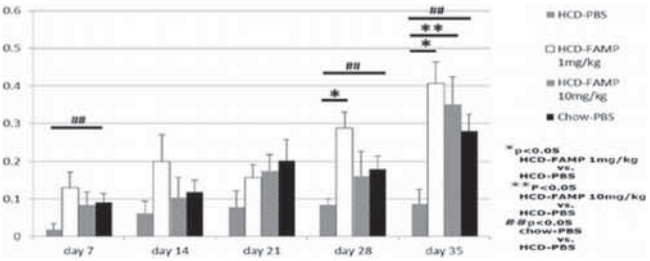
Purpose: We developed an apoA-I mimetic peptide FAMP which has high capacity of cholesterol efflux and enhances the function of HDL. The aim of this study is to show FAMP induces functionally important angiogenesis.
Methods: We examined the effect of FAMP on eNOS phosphorylation and tube formation of human aortic endothelial cells (HAoECs) in vitro and ischemia induced angiogenesis in vivo in mouse model of hind limb ischemia. Before ischemia surgery we fed mice with high-cholesterol diet (HCD) for 7 weeks to cause the endothelial dysfunction and to impair the HDL function. Mice were also assessed for functional recovery after hind limb ischemia by determining the body speed of a step cycle of a specific paw.
Results: FAMP significantly promoted the tube formation of HAoECs, and activated phospho-Akt at serine residue 473 and phospho-eNOS at serine residue 1177. The nitric oxide synthase inhibitor L-NAME inhibited the effect of FAMP on HAoECs. In hind limb ischemia model mice with high-cholesterol diet FAMP treatment showed significant improvement of blood perfusion recovery and increased CD-31 positive endothelial cells number compared with the control (figure). In addition, functional recovery of the FAMP group at 7 days after the induction of hind limb ischemia was greater than control. On the other hand, there was no beneficial effect of FAMP in eNOS-deficient mice.



Conclusions: Results of the present study indicate that FAMP treatment lead to angiogenesis and functional recovery in ischemic limbs of mice fed high-cholesterol diet through activation of nitric oxide (NO)-related pathway.

5739 | BENCH
TTC39B, a novel gene influencing HDL cholesterol levels - Ttc39b deficiency enhanced intestinal abca1, increased HDL cholesterol levels and reduced atherosclerosis -

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TTC39B, encoding tetratricopeptide repeat domain 39B(T39), was identified in genome wide association studies (GWAS) as a novel gene influencing HDL-cholesterol (HDL-C) levels. Although GWAS was initially used for finding genetic differences in a case-control design for particular diseases, its use quickly spread to traits measured on a continuum such as serum lipid levels. In fact, several studies published in 2009 revealed newly identified loci associated with levels of HDL-C, LDL-C and/or triglycerides and allowed many researchers including us to challenge to explore for a novel regulatory pathway for lipoprotein metabolism and atherosclerosis. T39 had not been previously implicated in lipoprotein metabolism at all and anything were unknown well, we decided to convert these information into animal models. We have now verified increased HDL-C levels in T39–/– mice. On a chow diet HDL-C levels were significantly increased by 22% and there were increases in LXR protein but not mRNA, increased expression of Abca1 mRNA and protein and increased secretion of HDL by small intestinal enterocytes. When mice were challenged with a high fat/high cholesterol/bile salt diet, there was a significant 42% increase in HDL-C and also decreased incorporation of dietary cholesterol and fat into chylomicrons and marked protection from steato-hepatitis. Ldlr–/–T39–/– mice on the Western diet showed increased HDL-C, decreased V/LDL cholesterol and decreased atherosclerosis. These studies show that T39 deficiency results in increased LXR primarily in enterocytes, beneficial lipoprotein changes and reduced atherosclerosis. Moreover, T39–/– mice are protected from fatty liver, indicating that T39 inhibition could be an effective strategy for reducing atherosclerosis and fatty liver.

5740 | BENCH
Orphan receptor GPRC5b activates inflammatory signaling in vascular smooth muscle cells

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Purpose: Atherosclerosis is driven by an inflammatory process of the vascular wall. GPRC5b, a novel orphan G protein-coupled receptor (GPCR), is endogenously expressed in cells of the vascular wall, including vascular smooth muscle cells (VSMC), endothelia cells (EC) and macrophages. In drosophila, the GPRC5b ortholog is glucose (Gluc)-responsive and regulates Gluc-induced energy and lipid metabolism. Our hypothesis is that GPRC5b is involved in pro-inflammatory and pro-atherogenic signaling, particulary in hyperglycemia.
Results: Confocal microscopy demonstrated specific accumulation of overexpressed YFP-tagged GPRC5b at the plasmamembrane of murine VSMC and EC. Incubation with high Gluc (25mM) instead of low Gluc (5mM) for up to 20 min induced an internalization of GPRC5b, which is a characteristic feature of GPCR in response to their cognate ligand. The adenoviral overexpression of human GPRC5b in VSMCs activated nuclear factor kappa B (NFκB) 72 h post infection (17±10-fold, $p<0.05$, n=4) compared to EGFP control even at low Gluc. Increasing the Gluc concentration up to 25mM further enhanced NFκB activity by 2-fold. GPRC5B overexpression in VSMCs caused a strong enhancement of the monocyte chemoattractant protein-1 (MCP-1) expression in the presence of high Gluc (25 mM) compared to EGFP control cells with the maximum detected after 4 h Gluc presence (GPRC5b: 202%±19% vs. EGFP 50%±7.5%, $p<0.05$, n=4). MAP-kinase Erk1/2 phosphorylation was increased in GPRC5b overexpressing cells compared to EGFP control cells in a Gluc-dependent manner (Gluc 0 min: +266%±45%; Gluc 90 min: +345±56%, $p<0.05$, n=3). Furthermore, the expression of GPRC5b is regulated by Gluc and the inflammatory cytokine TNFα: Both, stimulation with high Gluc concentrations (25mM) and TNFα (10ng/ml) induced an up to 5-fold increase in the GPRC5b mRNA content in VSMCs and ECs after 12 and 24 hours.
Conclusion: Our data suggest that GPRC5b causes a significant inflammatory response in VSMCs. Both, activity and expression of GPRC5b are regulated by Gluc and TNFα. Therefore, GPRC5b might play an important role in hyperglycemia-accelerated vascular inflammation and pathogenesis of atherosclerosis.

5741 | BENCH
HIF-1alpha mediated metabolic reprogramming critically regulates macrophage function in inflammatory conditions

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Background: Hypoxia is a pathological condition in which the tissue is deprived of adequate oxygen supply. It occurs in many cardiovascular diseases such as myocardial ischemia and atherosclerosis. Each cell exerts its own responses to hypoxia, and most of them are mediated through a transcription factor, hypoxia inducible factor 1α (HIF-1α). Macrophage, a key mediator of inflammation, accumulates in hypoxic area, and HIF-1a mediated hypoxic responses of macrophage strongly accelerate the inflammation processes. While both hypoxia and LPS induce HIF-1α protein accumulation, the distinctive functions of HIF-1α under inflammatory conditions still remain unclear.
Method: We investigated the genome wide binding profiles of HIF-1α in hypoxia or LPS treated macrophages by chromatin immunoprecipitation (ChIP) sequence, and the gene expression profiles of macrophage treated with each stimulus by RNA sequence. The metabolic states of such activated macrophages were analyzed with the Extracellular Flux Analyzer.
Result: ChIP-seq assay showed that hypoxia induced 2101 HIF-1α binding sites, whereas LPS elicited HIF-1α binding at 1396 sites. The comparing investigation of these data revealed most of HIF-1α binding sites of LPS treated macrophages were included in that of hypoxic macrophages (961/1396 sites). While hypoxia elicited HIF-1α bindings to the regulatory regions of genes related to glycolysis, angiogenesis and chromatin remodeling, LPS induced HIF-1α binding sites were confined to glycolytic enzymes.
To examine the roles of HIF-1α in macrophage activation, we analyzed the gene expression profiles of LPS treated wild-type and HIF-1α deficient macrophages. RNA-seq and gene ontology analysis demonstrated that LPS induced HIF-1α played a critical role in the expression of glycolytic enzymes.
Metabolic assays with the Extracellular Flux Analyzer showed that metabolic reprogramming (from aerobic to anaerobic) in LPS treated macrophages was totally dependent on HIF-1α. And interventions in the reprogramming by enzyme inhibitors (e.g. dichloroacetate) crucially affected gene expression and cellular function of LPS treated macrophage.
Conclusion: LPS induced HIF-1α bindings were significantly enriched for the elements related to glycolytic gene, and HIF-1α mediated metabolic reprogramming could play a critical role in macrophage activation.

5742 | BEDSIDE

Epigenetic signatures induced by methyltransferase Set7 drive endothelial dysfunction and vascular inflammation in patients with type 2 diabetes

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Purpose: In vitro studies have shown that mammalian methyltransferase Set7 mediates hyperglycemia-induced endothelial inflammation via epigenetic regulation of the transcription factor NF-kB. The link between Set7 and vascular disease in patients with type 2 diabetes (T2DM) remains to be elucidated. This study was designed to investigate whether Set7 contributes to endothelial dysfunction and vascular inflammation in T2DM patients.
Methods: Set7-related epigenetic changes on NF-kB p65 promoter were assessed in peripheral blood monocytes (PBM) isolated from 30 patients with T2DM and 20 age-matched controls. Chromatin immunoprecipitation assay (ChIP) was performed to investigate Set7-dependent epigenetic changes on human NF-kB promoter. Brachial artery flow-mediated dilation (FMD), urinary 8-isoprostaglandin F2α (8-isoPGF2α), expression of NF-kB downstream genes COX-2 and iNOS as well as plasma adhesion molecules VCAM-1, ICAM-1 and MCP-1 were also determined. Experiments in human aortic endothelial cells (HAECs) exposed to high glucose were performed to characterize the mechanisms of Set7-induced inflammation and oxidative stress. Between-variable correlations were measured by Spearman's analysis. Probability values less than 0.05 were considered statistically significant. Data are expressed as percentage of control (%).
Results: Set7 expression was increased in PBM from T2DM as compared with controls (275$\pm$18% vs. controls, $p<0.01$). Set7-dependent monomethylation of histone 3 at lysine 4 (H3K4m) was found on NF-kB p65 promoter of T2DM patients. This epigenetic mark was associated with upregulation of NF-kB-dependent pro-oxidant (COX-2, iNOS) and inflammatory genes (VCAM-1, ICAM-1 and MCP-1). Indeed, Set7 positively correlated with gene expression of COX-2 ($r=0.40$, $p<0.05$), iNOS ($r=0.47$, $p<0.05$), VCAM-1 ($r=0.67$, $p<0.01$), ICAM-1 ($r=0.58$, $p<0.01$) and MCP-1 ($r=0.53$, $p<0.01$). In line with these findings, Set7 expression correlated with oxidative marker 8-isoPGF2α ($r=0.44$, $p<0.05$) and brachial artery FMD ($r=-0.54$, $p<0.01$). In HAECs, gene silencing of Set7 suppressed H3K4m, NF-kB p65 expression and subsequent overexpression of oxidant and inflammatory genes.
Conclusions: Our findings demonstrate that a specific epigenetic signature induced by Set7 regulates NF-kB p65 expression, leading to dysregulation of oxidant and inflammatory genes and subsequent endothelial dysfunction. These results suggest that targeting Set7 may represent a promising approach to reduce oxidative and inflammatory burden in patients with T2DM.

TRANSLATIONAL RESEARCH AND HOT CLINICAL TOPICS IN CARDIOMYOPATHIES

5756 | BEDSIDE

Prevalence and clinical relevance of left ventricular outflow tract obstruction in patients with takotsubo cardiomyopathy

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Purpose: Takotsubo cardiomyopathy (TTC) is regarded a benign disease since left ventricular function returns to normal within a short time. However, a number of complications have been observed in patients (pts) with this enigmatic syndrome.
The present study evaluated the frequency and clinical relevance of left ventricular outflow tract obstruction (LVOTO) in a large TTC registry.
Methods: From 37 heart centres, 324 pts (296 f, 28 m, age 68$\pm$12) were included in a TTC registry according to the following criteria: 1) acute chest symptoms, 2) ischemic ECG changes, 3) reversible LV akinesia not corresponding to a single coronary artery territory, 4) absence of coronary artery stenoses. Complete data on complications were available in the last 209 registry pts.
Results: Complications developed in 108/209 pts (52%) within 2.6$\pm$2.9 days after symptom onset; 51 of these pts (24%) experienced >1 and 23 (11%) >2 complications. Most complications (77%) occurred within 3 days after symptom onset, however, 23% developed later (day 4 to 56).
During the acute phase, LVOTO (ranging from 20-100 mm Hg) was present in 10/209 pts (5%). LVOTO occurred within the first 2 days after hospital admission in 7 pts (70%) and developed between day 3 and day 10 in 3 pts. Inotropic agents had been administered in 1 pt. Age, sex and symptoms were comparable in pts with or without LVOTO. The ECG on admission showed a higher heart rate in association with LVOTO (101$\pm$15/min vs 87$\pm$23/ min, p=0.05). Other ECG parameters (ST elevation, T wave inversion, Q wave, QTc) were not different. Cardiac markers were lower with LVOTO (CK 1.67$\pm$1.2 vs 1.97$\pm$4.1 x upper limit of normal, Troponin 11.7$\pm$9.4 vs 21.4$\pm$56.3 x upper limit of normal, p=0.05). Angiographic ejection fraction was comparable in both groups (50$\pm$14% vs 51$\pm$15%), and LVOTO occurred with similar frequency in mid-ventricular and in apical ballooning (2/76 vs 8/133, p=ns). Transient mitral regurgitation ($\geq$ grade II) was only seen in pts with LVOTO (2/10 vs 0/199, $p<0.002$). RV involvement occurred only in pts without LVOTO (0/10 vs 48/199, p=0.06). Other complications (LV thrombus, pulmonary edema, ventricular tachycardia, shock, death) were observed with similar frequency in both groups. Receiving betablocker therapy LVOTO resolved within 2–3 days in every patient.
Conclusion: LVOTO occurs in 5% of pts with TTC and may be associated with high grade mitral regurgitation. Since catecholamines can provoke or aggravate LVOTO in TTC pts, inotropic agents should be used only under echocardiographic guidance. Spontaneously or under betablocker therapy LVOTO resolves within 2 to 3 days.

5757 | BEDSIDE

Prevalence of TTR senile cardiac amyloidosis among elderly patients with diastolic heart failure

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Introduction: Transthyretin (TTR) senile cardiac amyloidosis is usually not diagnosed as a cause of heart failure with preserved ejection fraction (HFPEF). Moreover, prevalence of TTR senile cardiac amyloidosis in this setting is unknown. Although no treatment has showed to improve survival in HFPEF patients, new drugs that stabilise TTR might be of use in this subset of patients. 99Tc-DPD scintigraphy has been shown to have a high sensitivity and specificity for the diagnosis of TTR cardiac amyloidosis.
Objective: We sought to determine the prevalence of TTR senile cardiac amyloidosis among elderly patients admitted due to HFPEF and to investigate if a 99Tc-DPD scintigraphy-based protocol is effective to diagnose TTR senile cardiac amyloidosis in this setting.
Methods: We prospectively recruited all consecutive patients $\geq$60 years old admitted due to HFPEF (LVEF$\geq$50%) with LV hypertrophy ($\geq$12mm) to the Departments Cardiology and Internal Medicine of our centre during a 28 months and a 9 months period respectively. All eligible patients were offered a 99Tc-DPD scintigraphy during hospitalization and their clinical data were collected.
Results: We recruited 122 patients (61% women, mean age 83$\pm$9 years, median NT-proBNP 4067pg/L (IQR 1471-9885), 56% admitted to Cardiology). 89 patients (73%) agreed to participate in the study and had a 99Tc-DPD scan done. No patient had any adverse event related to 99Tc-DPD scan. 15 patients (17%) showed intense uptake on 99Tc-DPD scintigraphy. All patients with a positive scan underwent genetic testing of TTR gene and no mutations were found. Moreover, an endomyocardial biopsy was performed in 3 patients confirming TTR amyloidosis. There was no significant difference in gender, history of hypertension, diabetes, AF, renal function or NT-proBNP between the 99Tc-DPDscan-positive group and negative group. Patients with TTR senile cardiac amyloidosis were significantly older, were more likely to have conduction disorders on ECG and have a permanent pacemaker, had lower voltage on ECG and higher wall thickness. There was no difference in the hypertrophic pattern neither in treatment between both groups.
Conclusions: Senile cardiac amyloidosis accounts for a significant number of diastolic heart failure cases and is probably underdiagnosed. A 99Tc-DPD scintigraphy-based protocol is safe and accurate to detect TTR senile cardiac amyloidosis among elderly patients admitted to hospital due to HFPEF.

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Genetic basis of familial dilated cardiomyopathy undergoing heart transplantation. A NGS study

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Introduction: Dilated Cardiomyopathy (DCM) is the most common cause of heart failure in the young and the most frequent cause of heart transplantation (HT). The high number of DCM-associated genes has made very difficult to study DCM by conventional genetic techniques. Moreover, genetic basis of DCM among patients undergoing HT is poorly characterized.
Purpose: We sought to determine the genetic basis of heart transplanted familial DCM and to establish the genetic uptake of modern NGS technologies in this setting.
Methods: 53 heart transplanted patients due to familial DCM underwent NGS

genetic evaluation with a panel of 195 genes related with cardiac conditions (64 specifically related with DCM). Genetic variants found were classified as possible pathogenic variants (novel missense variants in a previously DCM-associated gene and not present in controls) or as pathogenic mutations (previously described as pathogenic or variants found in a DCM-associated gene, not found in controls and predicting premature truncation, frameshift or abnormal splicing of the protein). Final pathogenicity status of possible pathogenic variants was determined by familial cosegregation studies.
Results: Initially, 28 pathogenic mutations were found in 23 patients (43%); 3 patients exhibited also possible pathogenic variants. 25 patients (47%) carried 29 possible pathogenic variants. 5 patients (9%) did not show any disease-causing mutations. Familial evaluation of 215 relatives confirmed pathogenicity in 13 patients with pathogenic mutations and allowed reclassification of possible pathogenic variants as pathogenic in 17 patients and as non-pathogenic in 3 cases. In 5 patients with possible pathogenic variants familial evaluation was inconclusive or not possible. At the end of the study the DCM-causing mutation was identified in 40 patients (75%). Mutated genes included: EMD (14 patients), TNN (10), BAG3 (4), DSP (3), LMNA (2), FLNC (2), MYBPC3, MYH7, TNNT2, DMD, FLNC, PKP2, DSC2, TPM1, TNNC1 and PSEN2. 5 patients (9%) harbor only possible pathogenic variants in the following genes: DSC2, MYBPC3, MYH6, MURC, MYPN, PSEN2, and TNNTC1. The causal mutation was not identified in 8 cases (15%).
Conclusions: Genetic spectrum of familial DCM undergoing heart transplantation is heterogeneous and multiple genes are involved. Current NGS technology plus detailed familial studies allow identification of causative mutations in the vast majority of familial DCM cases. Despite advances in genetic techniques, detailed familial studies remain critical to determine the pathogenicity of underlying genetic defects in a substantial number of cases.

5759 | BEDSIDE
Left ventricular systolic function but not the presence of late gadolinium enhancement independently predicts adverse cardiac events in muscular dystrophy patients

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Background: Cardiac involvement is a frequent finding in patients with X-linked recessive inherited muscular dystrophy type Duchenne (DMD) and Becker (BMD) and characterized by a myocarditis-like pattern of left ventricular (LV) myocardial fibrosis. It may be associated with dilated cardiomyopathy, progressive heart failure and arrhythmias, and represents an important cause of morbidity and mortality in this population.
Objective: Since the presence of myocardial fibrosis detected by late gadolinium enhancement (LGE) CMR was shown to be a strong and independent predictor of worse outcome in different non-ischemic myocardial diseases (such as myocarditis and dilative cardiomyopathy), we evaluated the prognostic value of different CMR parameters in patients with DMD/BMD.
Material and methods: Eighty-eight male MD (20 DMD and 68 BMD) patients (age 29±14yrs) were prospectively enrolled. All patients underwent cine- and LGE-CMR (1.5-Tesla) imaging at inclusion and were followed up for adverse cardiac events. The primary endpoint was considered cardiac death and/or cardiac transplantation. The secondary endpoint was a combination of hospitalization for heart failure, un-/sustained ventricular tachycardia (VT), ventricular fibrillation (VF) and/or (secondary prophylactic) ICD implantation.
Results: The mean follow-up time was 47±18 months. At study entry, the mean LV end-diastolic volume (LV-EDV) was 84±36 ml/m^2, the mean LV ejection fraction (LVEF) 53±14% and N=55 (63%) patients demonstrated an impaired LV systolic function. Presence of LGE was documented in N=56 (64%) patients with all of them showing a non-ischemic pattern of LGE. During follow-up, the primary endpoint was observed in three (3%) patients: two deaths and one heart transplantation. The secondary endpoint was encountered in 24 (27%) patients. Compared to patients without any events, those with a secondary endpoint were older (38±12yrs vs. 26±14yrs, p=0.001), had lower LVEF (39±12% vs. 58±12%, p<0.0001), increased LV-EDV (110±45ml/m^2 vs. 75±26ml/m^2, p<0.0001) and showed more frequently LGE presence (96% vs. 52%, p<0.0001). However, on multivariable analysis, LVEF was the only independent predictor for the secondary endpoint (OR, 95% CI: 0.93, 0.86-0.99, p=0.03).
Conclusion: In contrast to other non-ischemic myocardial pathologies, only the presence of an impaired LV systolic function, but not the presence of LGE per se, is an independent predictor for adverse cardiac events in patients with DMD/BMD. This finding is possibly due to different underlying pathomechanisms leading to myocardial damage in genetically vs. acquired cardiac diseases.

5760 | BEDSIDE
Targeted endomyocardial biopsy using electroanatomical voltage mapping for patients suspected of cardiac sarcoidosis

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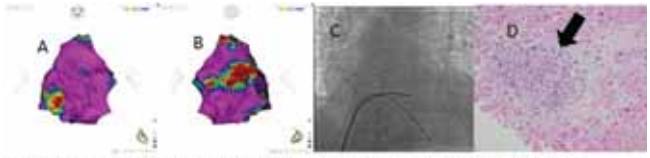
Purpose: Cardiac sarcoidosis (CS) may submit to life-threatening ventricular arrhythmias. Diagnosing CS is sometimes due to lack of typical signs, especially in isolated CS. Although histologic diagnosis is crucial, endomyocardial biopsy (EMB) is associated with low diagnostic yield caused by focal nature of the disease. We evaluated the diagnostic contribution of electroanatomical voltage mapping (EVM)-guided EMB in patients with CS.
Methods: We studied 8 consecutive patients (5 male, mean age 56±17 years, EF 40±18%) with a noninvasive probable diagnosis of CS according to current criteria (Japanese Diagnostic Standard and Guideline for Sarcoidosis 2006) and without specific histological findings of CS by traditional EMB. All patients underwent EVM-guided EMB.
Results: In all 8 patients, RV bipolar voltage mapping was performed with a 3-D electroanatomical mapping system (CARTO), and the low voltage area with 0.5-1.5 mV was identified at outflow tract and interventricular septum of the RV. Histological samples taken from the low voltage area by a standard biotome with telescoping two-directional long sheath technique showed typical histopathological findings of CS in 4 patients (50%) (The figure is a typical case of positive biopsy result). Positive biopsy sites were lower voltage and longer total activation time than negative biopsy sites (0.73 vs. 1.84 mV and 132 vs. 77 ms, respectively). No complication occurred throughout the procedure.



Electroanatomical bipolar voltage maps of the right ventricle displaying anterior (A) and posterior (B) view. (C) Fluoroscopic image of AP view showing biotome targeting the low-voltage lesion in the right ventricular septum. (D) Microscopic view of an endomyocardial biopsy specimen obtained from the right ventricular septum showing noncaseating granuloma (arrow).
A typical case of positive biopsy result.

Conclusions: EVM-guided EMB provides histological confirmations of sarcoidosis at high incidence, and is a safe and helpful in confirming the diagnosis of CS in probable CS patients who remain undiagnosed by traditional EMB.

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Tash in the elderly: a retrospective investigation in 1129 patients treated in a single centre

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Background: According to the 2012 AHA/ACCF guidelines TASH is recommended in particular for elderly patients with symptomatic HOCM. However only limited data exist, that report the safety and efficacy of alcohol ablation in elderly patients.
Methods: We retrospectively investigated the outcome after TASH in all patients who were treated in our hospital since 1996 and compared older patients of an age ≥75 years with younger patients <75 years.
Results: A total of 1129 consecutive patients (mean age 58,7 years) were analysed. 139 (12%) of these patients were older than 75 years. Older patients had a significantly higher NYHA functional class pre TASH (3.1±0.6 vs. 2.7±0.67; p<0.0001) and higher resting gradients at baseline (58.3±45.0mmHg vs. 50.4±35.7 mmHg; p=0.004). The amount of alcohol used in elderly patients was somewhat higher (1.65±1.41ml vs. 1.45±0.97ml; p=0.01), however, resulting in a comparable maximum CK activity after TASH (768.5±541.3U/l vs. 811.9±579.0U/l, P=0.493). Only 1 patient >75 years died in hospital due to an abrupt coronary no flow syndrome occurring during the intervention, which equals the mortality rate of the whole collective of 1.15%.
At six months follow up the NYHA functional class improved in both groups but did not differ from each other (1.73±0.79 vs. 1.41±0.83; p=0.302), however, older patients had a more pronounced gradient reduction compared to the younger patients (improvement rate of gradients at rest: -40.9±45.5 mmHg vs. -27.4±32.8 mmHg, p<0.002).
Conclusion: TASH is safe and effective even in the elderly. In contrast to other coronary interventions with an age dependent risk and outcome, TASH leads to favourable results with a very low mortality rate especially in elderly patients.

INTRACORONARY IMAGING: INSIGHTS

5774 | BEDSIDE
Comparison of vascular response after everolimus-eluting stents and bare metal stents implantation in ST-segment elevation myocardial infarction assessed by optical coherence tomography

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Background: Implantation of drug-eluting stents (DES) in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) reduces in-stent restenosis compared with bare metal stents (BMS), however, the long-term risk of DES use in STEMI has

been pointed. Previous pathological and optical coherence tomography (OCT) study reported that first generation DES use in STEMI resulted in higher rates of uncovered and malapposed stent struts at follow-up. The long-term safety of second generation everolimus-eluting stents (EES) use in STEMI remains unknown. We used OCT to examine vascular response including strut coverage and malapposition in patients with STEMI treated with EES and BMS.
Methods: We enrolled 102 patients with STEMI who underwent primary stenting and 10-month follow-up OCT (EES: 61 patients and BMS: 41 patients).
Results: A total of 21366 stent struts were analyzed. There were no significant differences in the percentage of uncovered and apposed struts and the percentage of uncovered and malapposed struts between 2 stents (1.6±2.3% versus 1.2±2.0%, P=0.379 and 0.6±1.2% versus 0.4±0.9%, P=0.596, respectively). The mean neointimal thickness was smaller in EES lesions (104±39 μm vs. 388±148 μm, P<0.001). Intra-stent thrombus was observed in 13% of EES lesions and 10% of BMS lesions (p=0.758). The frequencies of in-stent binary restenosis and target lesion revascularization were higher in EES compaed with BMS (3% vs. 17%, p=0.028 and 2% vs. 12%, p=0.037, respectively).
Conclusions: In STEMI patients undergoing primary PCI, there are no significant differences in the percentage of uncovered struts and malapposed struts, and the incidence of intra-stent thrombus at 10-month follow-up between EES and BMS. On the other hands, EES as compared with BMS significantly reduces neointimal hyperplasia. EES has a potential to achieve low late loss without sacrificing safety.

5775 | BEDSIDE
Saphenous vein graft changes after coronary artery bypass graft surgery: insights from the cardiac catheterization for bypass graft patency rate optimization (CABG-PRO) study

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Purpose: To investigate changes in saphenous vein graft (SVG) morphology during the first postoperative year using serial intravascular ultrasonography (IVUS) and optical coherence tomography (OCT).
Methods: IVUS and OCT measurements were performed in 13 and 10 SVGs, respectively, immediately after surgery and after 12 months. Minimum lumen diameter (minLD), lumen cross-sectional area (LCSA), vessel cross-sectional area (VCSA) were measured using the Echoplaque 4 software (Indec, Mountain View, CA). Wall thickness was calculated by the difference of average vessel lumen diameter and average lumen diameter divided by two. MinLD and LCSA were measured also for the OCT images with LightLab Imaging software (St Jude, Version D.0.2). The presence of thrombus and SVG valves was also evaluated.
Results: Compared to immediately after CABG IVUS imaging 12 months later revealed significant decrease in minLD (4.02±0.62 vs. 3.13±0.73 mm, p=0.0003), LCSA (14.56±4.58 vs. 9.10±4.67 mm^2, p=0.0005) and VSCA (22.08±4.68 vs. 18.45±4.99 mm^2, p=0.03), but increase in WT (0.50±0.09 vs. 0.74±0.17 mm, p=0.0007). These measurements correlated well with OCT measurements (baseline LCSA r2=0.84, p=0.0002 and follow-up LCSA r2=0.84, p=0.00002). OCT imaging revealed a double layered appearance of the SVG wall in all the study grafts (mean thickness 0.25mm ± 0.09mm) giving the impression of neointima formation within the original vein graft (figure 1). Additionally OCT demonstrated that the vein valves which were obvious in baseline images were fused into the graft wall one year post surgery.

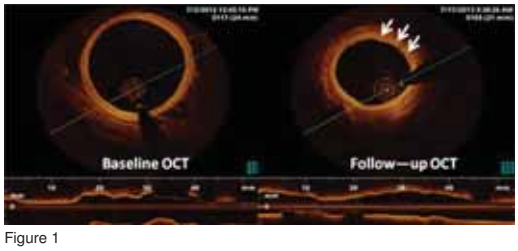

Figure 1

Conclusions: During the first year post CABG, SVGs undergo significant lumen loss due to a combination of wall thickening and negative remodeling. These findings provide important insights into the pathogenesis of early SVG failure.

5776 | BEDSIDE
Assessment of tissue prolapse after percutaneous coronary intervention and its relation with neointimal hyperplasia at follow-up by serial optical coherence tomography

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Purpose: Tissue prolapse (TP) after stent implantation is sometimes observed on optical coherence tomography (OCT). However, the clinical significance of TP after percutaneous coronary intervention (PCI) on long-term outcomes has not been fully investigated. Therefore, we sought to evaluate the relationship between TP after PCI and neointimal hyperplasia (NIH) at the follow-up period by serial OCT examination.
Methods: We evaluated 83 consecutive lesions in 83 consecutive patients (38 patients with acute coronary syndrome (ACS); 45 patients with stable angina pectoris (SAP)) that underwent PCI with OCT examination. All lesions were treated with stent implantation (44 lesions with drug-eluting stents (DES); 39 lesions with bare metal stents (BMS)). Plaque morphologies at the narrowest culprit sites on OCT were evaluated. TP after PCI was defined as tissue extrusion through the stent struts. TP area in each cross-sectional area (CSA) and TP volume calculated by adding the TP area in each CSA at 1-mm intervals throughout the stented segments were measured. At follow-up coronary angiography (mean interval: 8.2±2.2 months), NIH area in each CSA and NIH volume throughout the stented segments were also measured. The relationships between TP just after PCI and NIH at follow-up angiography at the culprit sites, at the most protruding sites, and throughout the stented segments were evaluated.
Results: TP area after PCI was correlated with lipid arc and fibrous cap thickness at the culprit sites (r=0.31, p=0.02 and r = -0.30, p=0.02) and at the most protruding sites (r=0.38, p=0.001 and r = -0.41, p=0.0002), respectively. In ACS lesions, TP area after PCI was correlated with NIH area at follow-up at the culprit sites (r=0.36, p=0.03) and at the most protruding sites (r=0.43, p=0.01). In SAP lesions, TP area at the most protruding sites was correlated with NIH area (r=0.46, p=0.005), but not at the culprit site (r=0.06, p=0.78). Furthermore, TP volume throughout the stented segment was correlated with NIH volume (r=0.43, p=0.0001) and TP ratio (TP volume/stent volume) was correlated with NIH ratio (NIH volume/stent volume) (r=0.31, p=0.006).
Conclusion: The extent of tissue prolapse observed on OCT after PCI was correlated with the underlying plaque morphologies and related with the degrees of neointimal hyperplasia at the follow-up period. Tissue prolapsed might influence the long-term stent outcomes.

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Clinical impact of intravascular ultrasound guidance in drug-eluting stent implantation for unprotected left main coronary disease: pooled analysis at patient level of 4 registries

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Purpose: We sought to investigate the clinical impact of the use of intravascular ultrasound (IVUS) during revascularization of patients with left main disease with drug-eluting stents (DES). Whether the use of IVUS during the procedure adds a clinical benefit remains unclear. There is only one previous observational study with relevant limitations supporting the value of this strategy.
Methods: We performed a patient level pooled analysis of 4 registries of patients with left main disease treated with DES in our country. A propensity score matching method was used to obtain matched pairs of patients with and without IVUS guidance.
Results: A total of 1,670 patients were included and 505 patients (30.2%) underwent DES implantation under IVUS guidance (IVUS group). By means of the matching method, 505 patients without the use of IVUS during revascularization were selected (no-IVUS group). Survival free of cardiac death, myocardial infarction and target lesion revascularization at 3 years was 88.7% in IVUS group and 83.6% in no-IVUS group (p=0.04) for overall population and 90% and 80.7% respectively (p=0.03) for the subgroups with distal left main lesions. The incidence of definite and probable thrombosis was significantly lower in IVUS group (0.6% vs. 2.2%; p=0.04). Finally, IVUS guided revascularization was identified as independent predictor for major adverse events in overall population (HR 0.70, 95% CI 0.52 – 0.99; p=0.04) and in the subgroup with distal lesions (HR 0.54, 95% CI 0.34 – 0.90; p=0.02).
Conclusions: The results of this pooled analysis show an association of IVUS guidance PCI with better outcomes in patients with left main disease undergoing revascularization with DES.

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Clinical and angiographic outcome of true versus false lumen stenting of coronary chronic total occlusions: Insights from intravascular ultrasound

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Purpose: We evaluated the in-hospital and long-term clinical and angiographic outcomes of drug-eluting stents (DES) deployed in true versus false lumen of successfully crossed chronic total occlusions (CTO)
Methods: Between August 2011 and October 2012, 158 consecutive patients

with 173 CTO lesions were scheduled for coronary intervention in a single center. All procedures were guided with intravascular ultrasound (IVUS). After successful guidewire crossing, lesions were classified according to IVUS evaluation into 2 groups; (1) true lumen group and, (2) subintimal stenting group; and compared with regards to in-hospital and long term clinical outcomes.
Results: In 154 lesions, DES were deployed in the true lumen; and in 19 (11%) lesions, DES were deployed in the subintimal space (95% confidence interval: 6.3% to 15.6%) with a success rate of 96% and 82.4%, in antegrade and retrograde approaches, respectively. IVUS showed that the prevalence of dissection was two times and intramural hematoma (IMH) was four times as higher in the subintimal stenting group ($p<0.001$ and $p<0.02$, respectively). Subintimal stenting was associated with a non-significant increase in Peri-procedural myocardial infarction (5.3% vs. 2.6%), major dissections (10.5% vs. 3.2%), and perforations (10.5 vs. 5.8%). Kaplan-Meier analysis revealed a similar rates of binary restenosis and target lesion revascularization between groups (p=0.73 and p=0.97, respectively). Six patients (4.2%) in the true lumen group and none in the subintimal group died at one year.

Table 1. IVUS findings of both subintimal and true lumen groups

	True lumen (n=154 lesions)	Subintimal stenting (n=19 lesions)	p value
Qualitative findings:			
Dissection flap, n (%)	64 (41.6)	16 (84.2)	<0.001
Dissected segment			
Proximal, n (%)	27 (17.5)	9 (47.4)	0.003
Distal, n (%)	24 (15.6)	5 (26.3)	0.02
Body, n (%)	13 (8.4)	2 (10.5)	0.29
Intramural hematoma, n (%)	8 (5.2)	4 (21)	0.02
Calcification (%)	141 (92)	16 (84)	0.08
Calcification morphology			
Superficial (%)	98 (64)	7 (37)	
Deep, n (%)	43 (28)	9 (47)	
Quantitative IVUS findings:			
Subintimal stenting length, mm	5.4 (4 to 9)	13.5±11.6	0.27
Dissection length, mm	274±132	4.2 (3 to 8.5)	0.68
Maximum arc of calcium, °	16±4.7	150±106	0.75
Proximal reference EEM CSA, mm^2	9.5±2.8	16±3.9	0.34
Proximal reference lumen CSA, mm^2	8±3	10±3	0.94
Distal reference EEM CSA, mm^2	5.3±2	8±2.9	0.23
Distal reference lumen CSA, mm^2		4.8±1.9	
Post-stent IVUS measurements:			
Mean stent CSA, mm^2	7±2	6.8±1.9	0.72
Stent expansion	0.86±0.35	0.90±0.28	0.55
Stent symmetry index	0.89±0.02	0.90±0.02	0.39

Values are mean ± SD, median (interquartile range), or n (%). CSA, cross-sectional area; EEM, external elastic membrane; IVUS, intravascular ultrasound.

Conclusions: Subintimal stent deployment in CTO segments, using second generation DES with IVUS guidance, carries a similar success rate, periprocedural complications, and long-term angiographic and clinical outcomes as true lumen stenting.

5779 | BEDSIDE
Sequential OCT evaluation of vessel response after bare metal stent implantation post-dilated with a paclitaxel-eluting balloon at 8-weeks and 6-months

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Background: The combination of a bare metal stent (BMS) with a drug-eluting balloon (DEB) seems interesting, since it combines the mechanics of a stent cage with an antiproliferative drug applied in a "single-shot" fashion. We aimed to evaluate the time course of vessel healing after such a procedure.
Methods: 53 patients received treatment of a de-novo coronary lesion with a BMS post-dilated with the DEB SeQuent Please™. A novel OCT algorithm was applied to analyze strut apposition, coverage, proliferation and vessel remodeling (remodeling volume =stented vessel volume – stent volume). Incomplete stent apposition (ISA) volumes and surface areas, as well as proliferation parameters (relative proliferation volume, median proliferation area) were calculated.
Results: Six-months f/u with both, QCA and OCT was conducted in 25 patients and 8-weeks f/u in 16 patients. Sequential OCT analysis at 8 weeks and 6 months was available in 8 patients. After 8 weeks, OCT analysis revealed distinct positive remodeling of the vessel wall (4.9±5.9 mm^3 vs. 2.0±2.6 mm^3, p=0.034) leading to significant strut malapposition (total malapposed struts: 11.4±11.8% vs. 2.2±5.0%; p=0.001). At 6-month this phenomenon was reversible and in most patients no longer verifiable. Intraindivual analysis of the same stent (N=8) also showed significantly more ISA and uncovered struts at 8 weeks compared to 6-months f/u as well as a trend toward greater ISA volume and positive remodeling volume in this small patient group (Table 1). As expected, proliferation parameters were significantly higher after 6 months (Relative Proliferation Volume: 5.1±7.8 vs. 13.2±7.4 mm^3/cm, p=0.002)
Conclusion: The application of paclitaxel by a DEB induces a positive vessel remodeling in the target lesion, which is in combination with bare metal stenting disadvantegous since it creates pronounced stent strut malapposition. Therefore, shortening of dual antiplatelet therapy below 6-months following a BMS + DEB procedure should be strictly avoided.

PREDICTING OUTCOMES IN HEART FAILURE – WHAT IS NEW?

5785 | BEDSIDE
A novel risk score for predicting 30-day mortality in heart failure patients undergoing non-cardiac surgery

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Background: Heart failure is an established risk factor for poor outcomes in patients undergoing non-cardiac surgery; yet risk stratification of these patients remains a clinical challenge. We developed an index for 30-day mortality risk-prediction in this particular group.
Methods and results: All individuals with heart failure undergoing non-cardiac surgery between October 23, 2004 and October 31, 2011 from Danish administrative registers (n=16,827) were identified and randomly divided into derivation and validation cohorts (2:1 ratio). By stepwise logistic regression modeling, factors associated with 30-day mortality were chosen and combined in a weighted risk score. In total, 1,787 (10.6%) died within 30 days. 39 risk factors were considered and 24 were retained with $P<0.05$ by multivariable logistic modeling. Risk factors included age, male gender, emergent surgery, body mass index, non-ischemic etiology of heart failure, chronic obstructive pulmonary disease, prior acute myocardial infarction, renal disease, peripheral artery disease, cerebrovascular disease, atrial fibrillation, cancer surgery, use of insulin, statins, furosemide ≥80 mg/d, major orthopedic surgery, intra-abdominal surgery, plastic surgery, intracranial surgery, venous/lymphatic surgery, pulmonary surgery, and artery surgery. Mortality rates ranged from 1.0% (26/2729) for the lowest risk score to 57.1% (36/63) for the highest risk score. The model had good calibration and discrimination (c statistic 0.80, Hosmer and Lemeshow p=0.89 for validation cohort). A low risk score could with a specificity of 97.6% rule out mortality in 1320/1335 (98.9%) of the patients in validation cohort.
Conclusions: For patients with heart failure, this index can accurately identify those at low risk for perioperative mortality.

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Transient anemia also affects long-term prognosis in heart failure patients

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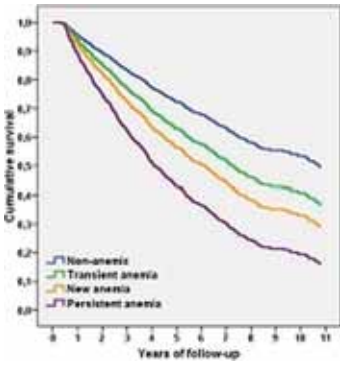
Background: It is well known that anaemia carries worse prognosis in heart failure (HF). Less evidence exists on how haemoglobin monitoring influences outcomes during long-term follow-up.
Aim: To examine whether serial haemoglobin levels measured 6 months apart have an impact on survival in a cohort of HF outpatients followed in a structured HF clinic. Haemoglobin (Hb) was determined at first visit and after 6 months. Anaemia was defined according to WHO criteria (Hb<13 g/dL for men and Hb<12 g/dL for women). Patients were classified relative to their Hb values as: non-anaemic (both determinations normal), transiently anaemic (anaemia at first visit but not at 6 months), newly anaemic (non-anaemia initially but anaemia at 6 months) and permanently anaemic (anaemia in both determinations).
Results: 1174 consecutive patients (71.7% men, mean age 66.8± years) were included in the study. The majority of patients were of ischemic aetiology (54%). Mean initial LVEF was 33% ± 13. Most patients were in NYHA class II (64.5%) or III (29.7%). Mean Hb was 12.8±1.9 at first visit and 12.8±1.7 at 6 months. According to the defined classification 477 patients (40.6%) were considered

Abstract 5779 – Table 1. Intraindividual comparison of same stent

	f/u (days)	Struts with ISA	Uncovered Struts	Maximal ISA Volume (mm^3)	Total ISA Volume (mm^3)	Positive Remodeling Volume (mm^3)
8-weeks f/u (n=8)	63.3±14.7	38.5±35.1	47.3±42.8	4.2±9.4	7.6±17.1	6.0±7.4
6-months f/u (n=8)	241.9±100.4	12.3±18.2	13.9±21.4	1.2±2.7	1.4±3.0	2.7±3.4
p-value	< 0.001*	0.012*	0.012*	0.093	0.069	0.063

f/u, follow-up; ISA, incomplete stent apposition.

non-anaemic, 170 (14.5%) had transient anaemia, 148 (12.6%) developed new anaemia and 380 (32.3%) were persistently anaemic. During a follow-up of 3.7±2.8 years after the 6 months visit, 495 patients died. Mortality was significantly higher in presence of any type of anaemia, although the worst prognosis was observed among those with persistent anaemia. Patients with transient anaemia, contrary to prior reports, also had worse prognosis than non-anaemic patients (figure).



Conclusions: Persistent, new, and even transient anaemia carry worse long-term prognosis in a large cohort of ambulatory HF patients.

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Nutritional status in outpatients with heart failure: a prognostic determinant beyond body mass index

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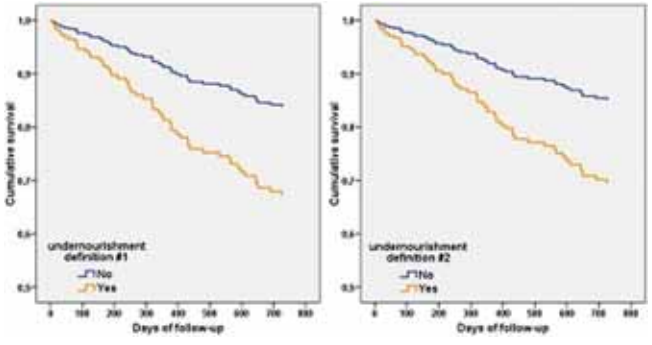
Background: Nutritional assessment may help to explain the repeatedly reported and non- completely understood obesity paradox in heart failure (HF) based on body mass index (BMI).
Objective: To assess the prognostic influence of undernourishment in HF outpatients.
Patients and methods: Two published definitions of undernourishment were used to assess 214 ambulatory HF patients (mean age 68.7±11.4 years, 75.2% male, 54.7% of ischemic etiology, LVEF 36.7±12.7). Definition #1 includes albumin, total lymphocyte count, tricipital skinfold (TS), subscapular skinfold (SS), and arm muscle circumference (AMC). Two or more below normal define undernourishment. Definition #2 only involves TS, AMC and albumin. One or more below normal define undernourishment. Patients were also stratified by BMI and percentage of body fat, and followed for two years. All cause death or HF hospitalization was the primary end-point.
Results: Among patients considered underweight based on BMI strata, 60% and 100% were undernourished by definitions #1 and #2, respectively; These figures were 31% and 44% among normal-weight, 4% and 11% among overweight, and 0% and 3% among obese patients, respectively. Undernourishment using both definitions was significantly associated with lower event-free survival. In multivariable analysis age, NYHA functional class, diabetes mellitus, NTproBNP, and undernourishment (HR 2.25 [1.11-4.56] and HR 2.24 [1.19-4.21] for definitions #1 and #2, respectively) remained in the model. In this cohort BMI and percentage of body fat did not independently predict event-free survival at two years.



Conclusion: Nutritional status has a very significant prognostic role in HF beyond BMI. Proper undernourishment assessment should become routine in HF patients.

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Atrial fibrillation and heart failure: meta-analysis of clinical outcomes in reduced versus preserved ejection fraction

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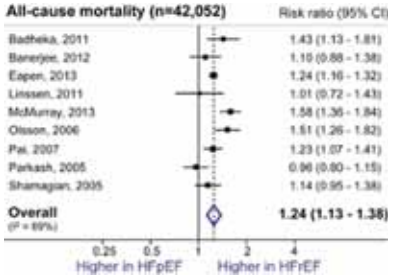
Purpose: Atrial fibrillation (AF) and heart failure frequently coexist, resulting in an overall increase in death and serious adverse clinical events. We compared cardiovascular outcomes in AF patients with reduced ejection fraction (HFrEF) and those with preserved ejection fraction (HFpEF) by performing a systematic review and meta-analysis.
Methods: A comprehensive literature search was performed for published studies, regardless of design. Pooled risk ratios (RR) were analysed using a random-effects model of unadjusted data. PROSPERO registration: CRD42014007305.
Results: 12 studies were included in the systematic review (n=53,885) with 9 suitable for meta-analysis (5 cohort studies and 4 sub-group analyses of randomised trials). The ejection fraction cut-off for HFpEF varied, including 40%, 50% and 55%. AF-HFrEF patients were younger, more often male and with a higher NYHA class. Oral anticoagulation use was 61% versus 56% for AF-HFpEF (p<0.001). All-cause mortality was significantly higher in AF-HFrEF (RR 1.24, 95% CI 1.13-1.38, p<0.001; 9 studies, n=42,052). Absolute death rates were 25.3% compared to 17.7% for AF-HFpEF during an average follow-up of 2 years. No differences were identified in incident stroke (RR 0.88, 95% CI 0.72-1.07, p=0.210; 6 studies, n=30,723), or other cardiovascular or bleeding outcomes. There was a marginally-significant excess of heart failure hospitalisation in HFrEF (RR 1.29, 95% CI 1.01-1.64, p=0.042; 4 studies, n=28,583).



AF & preserved/reduced ejection fraction.

Conclusion: Mortality is significantly higher in AF patients with HFrEF compared to HFpEF, although the overall rate of death remains high in both. Further action is warranted to standardise the diagnosis of HFpEF and to improve the rate of anticoagulation in all AF patients with heart failure.

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Predictors for the transition to de novo heart failure in stage B asymptomatic patients -A report from the CHART-2 Study-

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Background: Increasing prevalence of heart failure (HF) is an urgent public health issue worldwide. Although the clinical guidelines emphasize the importance to prevent the transition from asymptomatic to symptomatic HF, useful predictors for the development of de-novo HF in patients with cardiovascular disease remain to be elucidated.
Method: We analyzed the predictors for the development of de novo HF in 4,463 consecutive Stage B patients out of 10,219 patients registered in our Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) study. Stage B was defined as asymptomatic cardiac structural and/or functional diseases according to the ACC/AHA guidelines.
Results: Mean age was 67.3±12.4[SD] years old, and male patients accounted for 71%. Regarding etiologies for asymptomatic cardiac structural abnormalities, the prevalence of ischemic heart disease, valvular heart disease, and cardiomyopathy was 51, 19, and 10%, respectively. During the median follow-up period of 3.0 years, 280 deaths (6.0%) and 165 de novo HF requiring hospitalization (3.5%) were noted. A stepwise Cox regression analysis with Akaike's information criterion (AIC) revealed that development of de novo HF in Stage B patients could be predicted by age (hazard ratio (HR) 1.02, P=0.020), diastolic blood pressure (DBP) (HR 0.98, P=0.021), atrial fibrillation (AF) (HR 2.05, P<0.001), left ventricular (LV) diastolic diameter >50 (HR 1.58, P=0.035), LV ejection fraction ≤50% (HR 2.10, P=0.001), anemia (HR 1.73, P=0.005), chronic kidney disease (HR 1.70, P=0.007) and BNP levels (HR 1.04 (per 100 pg/ml), P=0.004). A Classification and Regression Tree analysis showed the first split point of BNP to discern development of de novo HF was 90.1 pg/ml. In a sub-analysis of 5 groups divided according to BNP levels (G1:<49, G2:50-89, G3:90-149, G4:150-199, G5:>200 pg/ml), the multivariate Cox proportional hazard model revealed that patients with BNP >90 pg/ml (G3, G4, G5) had significantly higher risk for de novo HF

compared with G1 (G2:HR 1.33, P=0.415, G3:HR 2.72, P=0.001, G4:HR 3.08, P=0.002, G5:HR 3.98, P<0.001).
Conclusions: These results indicate that several factors, including higher age, low DBP, AF, LV dysfunction, anemia, renal dysfunction and elevated BNP, could influence the progression from asymptomatic to symptomatic HF in Stage B patients, suggesting that management of these factors could prevent de novo HF in Stage B patients. In addition, BNP levels could be a useful predictor for de-novo HF in the real world clinical practice with a cut-off value of 90 pg/ml.

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Cardiac structure and function and prognosis in heart failure with preserved ejection fraction: Findings from the echocardiographic study of the TOPCAT trial

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Purpose: To determine the prognostic value of baseline cardiac structure and function for cardiovascular outcomes in heart failure with preserved ejection fraction (HFpEF).
Methods: Cardiac structure and function was assessed by echocardiography in a blinded core laboratory at baseline in 935 patients with HFpEF (ejection fraction [EF] ≥45%) enrolled in the TOPCAT trial and related to the primary composite outcome of CV death, HF hospitalization, or aborted cardiac arrest, and its components. Cox proportional hazard models adjusted for age, gender, race, enrollment region (Americas vs Russia/Georgia), randomization stratum, randomized treatment, heart rate, prior HF hospitalization, hematocrit, creatinine, atrial fibrillation, diabetes, and LVEF.
Results: At a median follow-up of 2.9 years, 244 patients experienced the primary outcome. LV hypertrophy was associated with the composite outcome and its components beyond baseline clinical and laboratory prognostic variables (adjusted HR 1.55, 95% CI 1.18-2.05, p=0.002), as were elevated filling pressure (E/E') and higher pulmonary pressures (tricuspid regurgitation [TR] velocity; Figure). Risk of adverse outcome associated with LVH was additive to the risk association with elevated E/E' (LVH alone: adjusted HR 2.0 [0.7-5.8], p=0.21; elevated E/E' alone: adj HR 2.0 [0.8-5.3], p=0.14; both: adj HR 3.6 [1.4-9.1], p=0.007).

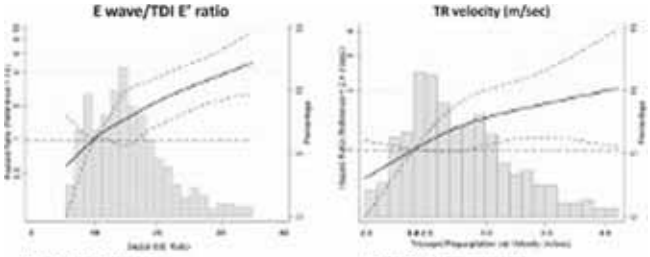

Figure: Splines of the unadjusted HR for the primary composite endpoint. Histograms show the population distribution of each measure.

Conclusions: Among HFpEF patients enrolled in TOPCAT, LVH, higher LV filling pressure, and higher pulmonary pressure were predictive of HF hospitalization, CV death, and the composite of these beyond clinical and laboratory predictors. These features identify HFpEF patients at particularly high risk for CV morbidity and mortality and may be used to target individuals within this heterogeneous syndrome in future studies.

NOVEL ASPECTS OF P2Y12 INHIBITION

5800 | BEDSIDE
Ticagrelor crushed tablets administration in STEMI patients: The Mashed Or Just Integral Tablets of ticagrelOr (MOJITO) study

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Purpose: The administration of clopidogrel in crushed form resulted in faster and greater bioavailability in healthy humans. Current ST-elevation myocardial infarction (STEMI) guidelines strongly recommend Ticagrelor. Of note, in STEMI patients residual platelet reactivity soon after a loading dose (LD) of ticagrelor has been shown to be higher than that reported for healthy volunteers. The aim of the study was to evaluate the superiority of Ticagrelor 180 mg crushed tablets versus Ticagrelor 180 mg integral tablets in decreasing residual platelet reactivity in patients undergoing primary percutaneous coronary intervention (PPCI).
Methods: Eighty-two consecutive patients with STEMI were randomized to receive Ticagrelor 180 mg as integral tablets (n=41) or as crushed tablets (n=41) before PPCI. The primary study end-point was residual platelet reactivity by P2Y12 Reactivity Units (PRU) VerifyNow 1 hour after ticagrelor LD. Secondary end-points were: 1) The percent of patients with a high residual platelet reactivity (HRPR, PRU ≥208) 1 hour and 2 hours after ticagrelor LD; 2) Major and minor bleedings (TIMI criteria); 3) Occurrence of dyspnoea or symptomatic bradycardia.
Results: PRU 1 hour after the LD was 168 (61-251) and 252 (167-301) in crushed and integral group, respectively (p=0.006). PRU values did not significantly differ between crushed and integral tablet groups at 2, 4 and 8 hours from LD (p= NS for all). HRPR was found in 35% and 63% patients (p=0.011) at 1 hour and in 20% and 28% patients (p=0.431) at 2 hours, respectively. There was no significant difference in bleeding, arrhythmias or dyspnea episodes in the 2 groups.
Conclusions: The administration of ticagrelor crushed tablets in STEMI patients is feasible and safe, and allow to achieve earlier platelet inhibition as compared with standard integral tablets.
ClinicalTrials.gov Identifier: NCT01992523

5801 | BEDSIDE
Reversibility of clopidogrel, prasugrel and ticagrelor- ex vivo study

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Background: In addition to clopidogrel (CL) two new P2Y12 inhibitors prasugrel (Pr) und ticagrelor (Ti) have been approved in ACS.
In contrast to Cl, Pr and Ti inhibit ADP-induced platelet activation more rapidly, more consistently and to a higher extend. Furthermore, in acute coronary syndromes Pr and Ti showed a significant reduction of major adverse cardiac events compared to clopidogrel, although increasing rates of bleedings. Compared to thienopyridenes, Ti needs no further metabolization and has a different binding site from ADP, making it an allosteric antagonist with reversible blockage of the P2Y12 receptor.
In case of acute bleedings or emergent surgical procedures, the platelet inhibitory effect has to been reversed rapidly.
Aim of this study was to examine ex vivo whether platelet inhibition induced by Cl, Pr and Ti could be reversed after administration of platelets. Furthermore, differences of Cl, Pr and Ti as well as the quantity of platelet transfusion in order to achieve normalization of platelet function should be determined.
Methods: 61 blood samples of patients with acute coronary syndromes (24hours after initial loading dose with Cl, Pr or Ti) have been investigated after administration of increasing amounts of platelet rich plasma (PRP) or pooled platelet concentrates (PP). The inhibition of the P2Y12-receptor was determined by Platelet Reactivity Index (PRI-VASP).
Results: Initial PRI-VASP values were within therapeutic range with significant lower levels in the Pr and Ti-groups compared to Cl (Pr 12,9±6,4%; Ti 18,3±13,2% and 32,3±13,3%; p<0,001 Pr/Ti vs. Cl). After addition of PRP a significant increase in all 3 groups could be determined (Cl 29,6±14,8% to 56,2±12,0%; p<0,001; Pr 12,9±6,4% to 46,5±12,7%, p<0,001; Ti 14,8±2,6% to 36,7±13,2%, p<0,001). The increase was less pronounced in the Ti-group.
After addition of PP there was also a significant increase of the PRI-VASP in the Cl and Pr-groups Prasugrel (37,1±9,4% to 56,4±6,2%; p=0,005; 12,9±6,9% to 44,8±9,1%; p<0,001). In the Ti group there was only a non-signifcant trend to higher PRI-VASP values (13,4±9,8% to 19,5±10,0%; p=0,542).
Conclusion: The present study demonstrated that addition of both PRP and PP ex vivo are effective to partially reverse the platelet inhibitory effect on the P2Y12-receptor, whereas this effect is lowest for ticagrelor. These results support the current practice to administrate platelets in acute bleedings or emergent surgical procederes. If this approach leads to a reduction of bleeding complications in vivo has to be proven in further clinical studies.

5802 | BEDSIDE
Similar risk of cardiovascular events in diabetic patients with acute coronary syndromes managed medically with prasugrel vs clopidogrel: findings from the TRILOGY ACS trial

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Purpose: A prior analysis of diabetic subjects in the TRITON trial presenting with acute coronary syndrome (ACS) and undergoing percutaneous coronary intervention (PCI) showed enhanced benefit with prasugrel vs clopidogrel, but the

Abstract 5802 – Table 1. Kaplan-Meier event rates at 30 months

Event	Diabetes: all patients		Diabetes: insulin-treated		Diabetes: not insulin-treated		No diabetes	
	Pras (n=1756)	Clopid (n=1783)	Pras (n=564)	Clopid (n=547)	Pras (n=1192)	Clopid (n=1236)	Pras (n=2899)	Clopid (n=2868)
CV death, MI, or stroke	24.0 (21.0–27.0)	25.6 (22.6–28.7)	31.2 (25.2–37.3)	39.1 (32.3–46.0)	20.5 (17.2–23.8)	19.3 (16.5–22.1)	15.5 (13.5–17.5)	17.0 (14.7–19.4)
CV death	14.1 (11.5–16.6)	13.8 (11.5–16.1)	16.9 (11.8–21.9)	18.2 (13.4–22.9)	12.7 (9.8–15.6)	11.7 (9.3–14.2)	7.4 (5.8–9.0)	8.0 (6.6–9.3)
MI	13.7 (11.4–15.9)	16.5 (13.7–19.2)	19.1 (14.2–23.9)	28.3 (21.5–35.2)	11.2 (8.8–13.5)	11.1 (8.8–13.3)	9.0 (7.6–10.4)	9.7 (7.6–11.8)
Stroke	2.3 (1.4–3.1)	3.2 (1.9–4.4)	2.8 (1.1–4.5)	5.7 (2.4–9.0)	2.0 (1.0–3.0)	2.1 (1.0–3.2)	2.2 (0.9–3.4)	2.2 (1.4–3.0)
All-cause death	16.4 (13.9–19.0)	15.8 (13.5–18.1)	20.7 (15.7–25.8)	20.7 (16.0–25.4)	14.3 (11.5–17.2)	13.5 (11.1–15.9)	8.7 (7.2–10.2)	9.9 (8.4–11.4)
GUSTO severe-life threatening bleeding	1.0 (0.1, 1.9)	0.9 (0.3, 1.5)	1.5 (0.0, 3.8)	1.1 (0.0, 2.3)	0.8 (0.0, 1.5)	0.8 (0.0, 1.5)	1.2 (0.2, 2.3)	1.1 (0.5, 1.7)

Data are presented as K-M rate (95% CI).

impact of this treatment comparison in medically managed ACS patients with diabetes remains uncertain.

Methods: The TRILOGY ACS trial compared prasugrel vs clopidogrel in non-ST-elevation ACS patients managed medically without revascularization. We compared baseline characteristics and treatment-related outcomes among 3539 patients with diabetes (1111 were treated with insulin) vs 5767 patients without diabetes.

Results: Patients with diabetes were younger, more commonly female, heavier, more likely to have known cardiovascular (CV) risk factors, and more frequently had a history of revascularization before the index ACS event compared with patients without diabetes. The frequency of ischemic events through 30 months was higher among patients with diabetes vs no diabetes; within the diabetic group, CV event frequency was higher among patients with insulin treatment vs those without (Table). No differences in bleeding rates were observed. All event rate comparisons by treatment (prasugrel vs clopidogrel) were statistically similar ($p>0.05$) except for a marginally lower rate of myocardial infarction with prasugrel vs clopidogrel among insulin-treated diabetic patients (p=0.044).

Conclusions: We observed a higher risk of ischemic events during long-term follow-up among patients with ACS and diabetes who were managed medically, but no significant treatment-related differences for ischemic and bleeding events with prasugrel vs clopidogrel were demonstrated.

5803 | BEDSIDE

Incidence and impact of dual antiplatelet therapy cessation among diabetic patients receiving drug eluting stents: a "real-world" analysis from the PARIS registry

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Purpose: The optimal duration of dual antiplatelet therapy (DAPT) and impact of DAPT cessation after percutaneous coronary intervention (PCI) with drug eluting stents (DES) in diabetic patients remains controversial.

Methods: The PARIS registry was a multicenter, prospective, observational study of patients undergoing PCI with stent implantation. The study was designed to examine the relationship between modes of DAPT cessation and adverse outcomes. Pre-specified categories of DAPT cessation included physician-guided discontinuation, temporary interruption (<14 days) for surgical reasons, and disruption due to non-adherence or bleeding. Associations between DAPT cessation and adverse events among diabetics were examined using Cox models with DAPT cessation as a time-updated variable.

Results: Among 5031 patients enrolled in the PARIS registry, we identified 1430 (33.0%) diabetic patients who received DES. During 2 year follow-up, the rates of any DAPT cessation, discontinuation, interruption and disruption were 50.2%, 32.6%, 11.5% and 12.4%, respectively. The cumulative incidence of major adverse cardiac events (MACE) was 9.2%, with most of these events occurring among those on (76.4%) versus off (23.6%) DAPT. While discontinuation or interruption was not associated with an increased risk for MACE, most adverse events were significantly increased after DAPT disruption (Table). There were 3 stent thrombosis events following an episode of DAPT cessation, all of which occurred after disruption.

	On DAPT (n=760)	Discontinuation (n=371)	Interruption (n=130)	Disruption (n=169)
Cardiac Death	1.0 (ref)	0.58 (0.17–2.02)	1.36 (0.41–4.57)	3.41 (1.73–6.70)
Spontaneous MI	1.0 (ref)	1.41 (0.55–3.62	1.36 (0.41–4.50)	2.80 (1.38–5.70)
Stent Thrombosis*	1.0 (ref)	N/A	N/A	3.53 (0.97–12.92)
MACE	1.0 (ref)	0.82 (0.37–1.78)	1.37 (0.59–3.23)	2.26 (1.30–3.93)

*Definite/probable. DAPT, dual antiplatelet therapy; MI, myocardial infarction; MACE, major adverse cardiac events. HR calculated from multivariate Cox model including the following covariates: age, gender, region, ACS, stent type, stent lenght, DAPT cessation.

Conclusions: Among diabetic patients receiving DES, most adverse events occur while patients are on rather than off DAPT. While discontinuation or brief interruption of DAPT appears safe among such patients, the risk following DAPT disruption remains substantial.

5804 | BEDSIDE

Cangrelor reduces large, prognostically important, myocardial infarctions in patients undergoing PCI: findings from CHAMPION-PHOENIX

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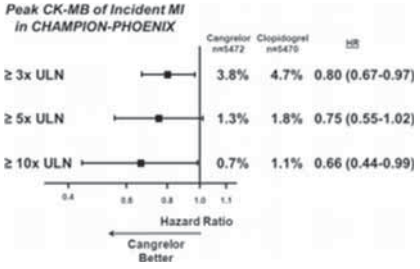
Purpose: Cangrelor is an intravenous P2Y12 inhibitor that reduces the composite rate of death, myocardial infarction (MI), ischemia-driven revascularization, or stent thrombosis in patients undergoing percutaneous coronary intervention (PCI) at 48 hours. We characterized the effects of cangrelor on the type and size of MI that occurred within 48 hours after randomization in the CHAMPION-PHOENIX trial.

Methods: 11,145 randomized patients were treated in a double blind, double dummy fashion with either cangrelor or a loading dose of clopidogrel. CK-MB was to be measured every 6 hours and analyzed by a core laboratory. An independent clinical events committee adjudicated all potential MI. The association of MI and 30-day mortality was modeled with adjustment for known predictors of death. MI was further classified into type and size.

Results: A total of 462 patients (4.1%) undergoing PCI had a MI within 48 hours following randomization. The majority of MI were peri-procedural (Type 4a) (n=433, 94%). Cangrelor, as compared with clopidogrel, reduced MI with an elevation of CK-MB ≥3x ULN by 20% (3.8% vs. 4.7%, HR 0.80, 95% CI 0.67-0.97). There were consistent effects on MI with a 25% reduction in MI with CK-MB ≥5x ULN and a 34% reduction in MI with CK-MB ≥10x ULN (Figure). The occurrence of MI with a rise in CK-MB ≥3x, ≥5x, and ≥10x ULN was associated with increased odds of 30-day mortality (ORadj 6.7 [95% CI 3.2, 14.1], 9.0 [95% CI 4.3, 18.7], and 10.1 [95% CI 4.2, 24.5], respectively).



Conclusions: In patients undergoing PCI, the occurrence of periprocedural MI was associated with significant risk of death. Cangrelor, when compared with clopidogrel, significantly reduces MI, including large MI.

5805 | BENCH

Ticagrelor and dipyridamole potentiate adenosine-induced stimulation of neutrophil chemotaxis in the presence of erythrocytes

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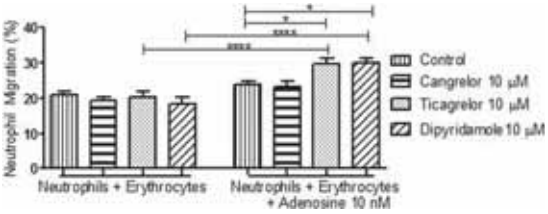
Introduction: Ticagrelor is a dual inhibitor of platelet P2Y12 receptors and cellular adenosine reuptake. In the PLATO study, ticagrelor was associated with fewer pulmonary infections in ACS patients compared to clopidogrel. We studied whether adenosine reuptake inhibition by ticagrelor and another adenosine reuptake inhibitor, dipyridamole, might influence leukocyte function.

Methods: Neutrophils and erythrocytes were isolated from healthy volunteers using Histopaque ficoll gradient centrifugation. Concentration-dependent effects of adenosine on neutrophil chemotaxis were investigated and the involved adenosine receptors were identified using adenosine receptor antagonists. The effects of cangrelor (another P2Y12 inhibitor), ticagrelor and dipyridamole on IL-8-stimulated neutrophil chemotaxis were determined over 30 minutes in the presence or absence of i) erythrocytes and/or ii) adenosine.

Results: Low-concentration adenosine (10 nM) caused a significant increase in neutrophil chemotaxis (28.7 ± 4.4vs. 22.6 ± 2.4; $P<0.01$) in response to IL-8 through the low-affinity A1 receptor, whereas the high-affinity receptor A2a could reverse this action in the presence of higher-concentration adenosine 10 μM (22.8 ± 3.6 vs. 31.5 ± 8.0; $P<0.05$). Erythrocytes attenuated the effects of adeno-



sine on neutrophil chemotaxis in the presence of cangrelor or control whereas ticagrelor and dipyridamole both preserved this effect of adenosine in the presence of erythrocytes (Figure).

Conclusion: Inhibition of adenosine reuptake by ticagrelor and dipyridamole leads to potentiation of the effects of adenosine on neutrophil chemotaxis in the presence of erythrocytes. This represents a potential mechanism by which ticagrelor could influence host defence against bacterial lung infection.

RISK ASSESSMENT IN ATRIAL FIBRILLATION: WHAT REALLY MATTERS?

5831 | BEDSIDE
Stroke is often the first clinical manifestation of atrial fibrillation. The FibStroke study

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Purpose: Atrial fibrillation (AF) is often asymptomatic and may remain undiagnosed and lead to stroke when no anticoagulation is used.

Methods: We analyzed the timing of 1,471 ischemic strokes and transient ischemic attacks (TIA) in relation to the diagnosis AF in 1,310 patients treated in 4 centers during 2003-2012. The patients were divided into 2 groups according to the history of AF: (1) patients with a history of AF and (2) patients with a new diagnosis of AF at the presentation of stroke or TIA.

Results: AF was diagnosed for the first time at the time of stroke/TIA in 384 (26.1%) patients. Patients with a history of AF were significantly older and they had more often heart failure, vascular disease, history of stroke and chronic AF (Table).

Clinical characteristics

	Previous AF n (%)	New AF n (%)	p
N (% of all events)	1087 (73.9)	384 (26.1)	
Age, yr (95% CI)	76.7 (9.3)	74.8 (9.3)	0.001
Female gender	601 (55.3)	204 (53.1)	0.5
Heart failure	221 (20.3)	37 (9.6)	<0.001
Diabetes	241 (22.2)	76 (19.8)	0.3
Hypertension	698 (64.2)	245 (63.8)	0.9
Vascular disease	432 (39.7)	91 (23.7)	<0.001
History of stroke	359 (33.0)	60 (15.6)	<0.001
Paroxysmal AF	406 (44.0)	197 (80.1)	<0.001

Conclusions: Stroke is often the first manifestation of AF. More effective measures to screen for asymptomatic AF are needed.

5832 | BEDSIDE
Cost-effectiveness analysis of screening for atrial fibrillation in pharmacies using an iPhone handheld ECG (SEARCH-AF)

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Purpose: Identifying unknown atrial fibrillation (AF) in the community and subsequent anti-thrombotic treatment could reduce stroke burden. We aimed to determine the cost-effectiveness of community screening for unknown AF, using an iPhone ECG with an automated algorithm (iECG) in pharmacies.

Methods: Cost-effectiveness analysis from an Australian health funder perspective comparing cost of iECG population-based AF screening, to diagnosed AF in an unscreened population, for age 65-84. Results are expressed as incremental cost-effectiveness ratio (ICER) per stroke avoided and per quality adjusted life year (QALY) gained. The model assumed a rate of unknown AF of 1.4% in target population; test sensitivity 97%; test specificity 92%; cost of warfarin treatment and monitoring $AUD803.80 (€421.73) pa; cost per screen $AUD20 (€10.49); and 5.09 QALYs gained per stroke avoided. Benefits of detecting AF are based on data obtained from the UK Clinical Practice Research Datalink using a subset of 5,567 patients with incidentally detected asymptomatic AF, with incidence rates projected out to 10 years following initial screen. Sensitivity analyses varied base assumptions for anticoagulant guideline-adherence rate.

Results: The ICER of extending iECG screening into the community, based on 55% warfarin prescription adherence, would be $AUD5,951 (€3,122) per QALY gained and $AUD30,290 (€15,892) for prevention of one stroke. Sensitivity analysis indicated cost-effectiveness improved with increased treatment adherence.

Conclusions: Screening with iECG in pharmacies is cost effective for stroke prevention and gaining QALY, and well within a range fundable on a population basis, using either warfarin or novel oral anticoagulants. Guideline recommendation of community iECG screening for AF should be considered.

5833 | BEDSIDE
Comparison of ATRIA and CHA2DS2-VASc risk stratification schemes for the prediction of stroke in the individual patient with atrial fibrillation and the impact on treatment decisions

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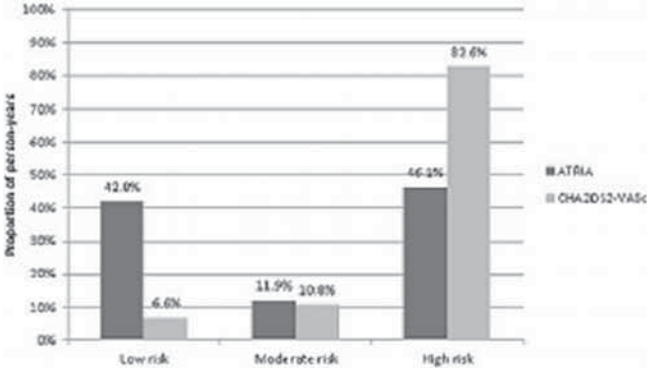
Purpose: To compare the predictive ability of the currently recommended CHA2DS2-VASc ischaemic stroke risk score with the new ATRIA stroke risk score in patients with atrial fibrillation (AF).

Methods: Patients with AF, not using warfarin, were assembled from the Clinical Practice Research Datalink (CPRD) database. Patients were followed from date of AF diagnosis until occurrence of ischaemic stroke, prescription of warfarin, death or the end of study. Independent predictors of ischaemic stroke were identified with a Cox proportional hazard model by stepwise backward selection. The c-index assessed the discriminative ability of the risk schemes. Net reclassification improvement (NRI) assessed net correct risk reclassification using ATRIA versus CHA2DS2-VASc, using published point score cut-offs. As correct stroke risk thresholds for low/moderate/high risk, 1% and 2% per year were used.

Results: We included 60,594 patients. The overall stroke rate was 2.45% per year. Age and previous stroke were the strongest predictors of ischaemic stroke. Other independent predictors were hypertension (HR 1.25 CI 95%, 1.15-1.35) and diabetes (HR 1.27 CI 95%, 1.14-1.41). Vascular disease and heart failure were not significant predictors. For the full point scores, the c-index was 0.71 (CI 95%, 0.70-0.72) for the ATRIA score and 0.69 (CI 95%, 0.68-0.70) for the CHA2DS2-VASc score. The NRI was 0.38 for ATRIA compared to the CHA2DS2-VASc-score, resulting entirely from downward reclassification (Figure).



Distribution of personyears by risk cat.

Conclusion: The ATRIA score had better discriminative ability than CHA2DS2-VASc. The CHA2DS2-VASc-score assigns most AF patients to the moderate and high risk categories, which could lead to overtreatment. In this community-based, low-risk cohort, the ATRIA score correctly reclassified patients as lower risk.

Abstract 5832 – Table 1. Sensitivity analysis (ICER/QALY gained)

ASSUMPTIONS	40% Rx adherence	50% Rx adherence	55% Rx adherence	60% Rx adherence	70% Rx adherence	80% Rx adherence
Base case	$8,457	$6,619	$5,951	$5,394	$4,519	$3,862
DEVIATIONS FROM BASE CASE: *$AUD30 per screen	$11,578	$9,116	$8,221	$7,474	$6,302	$5,423
*Treatment: 90% NOAC @ $1,508pa and 10% warfarin	$16,512	$14,674	$14,006	$13,449	$12,574	$11,918
*Treatment: 90% NOAC @ $1,174pa and 10% warfarin	$12,696	$10,858	$10,189	$9,632	$8,757	$8,101
*4.275 QALYs gained per stroke avoided	$10,070	$7,881	$7,085	$6,422	$5,380	$4,599
*6.39 QALYs gained per stroke avoided	$6,737	$5,273	$4,740	$4,297	$3,600	$3,077

Rx: Treatment; NOAC: novel oral anticoagulant; $: $AUD (Purchasing Power Parity: $AUD1=€0.5247).

5834 | BEDSIDE

Using the CHA2DS2-VASc score for refining stroke risk stratification in low-risk Asian patients (ATRIA score 0-5) with atrial fibrillation

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Background: A new scoring system, ATRIA score, was proposed for risk stratification in patients with atrial fibrillation (AF). Whether the ATRIA scheme can adequately identify patients who are at low-risk of ischemic stroke remains unknown. The goal of the present study was to compare the performance of ATRIA and CHA2DS2-VASc scores for stroke prediction.
Methods: This study used the "National Health Insurance Research Database" in Taiwan. A total of 186,570 AF patients without any antithrombotic therapy were selected as the study cohort. The clinical endpoint was the occurrence of ischemic stroke.
Results: During the follow-up of 3.4±3.7 years, 23,723 patients (12.7%) experienced ischemic stroke. The CHA2DS2-VASc score performed better than ATRIA score in predicting ischemic stroke as assessed by c-indexes (0.698 versus 0.627, $p<0.0001$). The CHA2DS2-VASc score also improved the net reclassification index by 11.7% compared with ATRIA score ($p<0.0001$). Among 73,242 patients categorized as "low risk" based on an ATRIA score of 0-5, the CHA2DS2-VASc scores ranged from 0-7 and annual stroke rates ranged from 1.06% to 13.3% at one-year follow-up, and from 1.15% to 8.0% at 15-year follow-up. The Kaplan-Meier estimates of probability of remaining free of ischemic stroke according to the CHA2DS2-VASc score are illustrated in Figure 1. The c-indexes of CHA2DS2-VASc score (0.629) was significantly higher than that of ATRIA score (0.593) in this "low-risk" category.

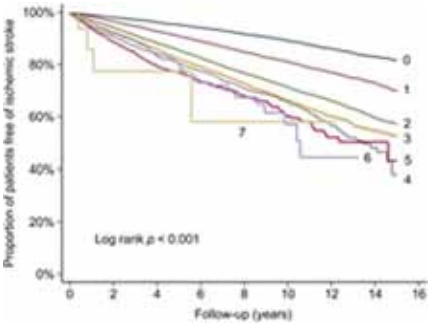

Figure 1. KM curve.

Conclusions: Patients categorized as "low risk" using an ATRIA score were not necessarily "low risk", and the annual stroke rates can be as high as 2.95% at 1-year follow-up and 2.84% at 15-year follow-up. In contrast, patients with a CHA2DS2-VASc score of 0 had a "truly low risk" of ischemic stroke, with an annual stroke rate around 1%.

5835 | BEDSIDE

Patients with native aortic stenosis represent a high-risk subgroup in nonvalvular atrial fibrillation - Results from ROCKET AF

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Background: ROCKET AF included patients (pts) with nonvalvular atrial fibrillation (AF) defined as the absence of mitral stenosis or artificial valve prostheses which allowed the inclusion of pts with native aortic stenosis (AS).
Aim: To compare characteristics and outcomes of pts with AS and pts without significant valvular disease (SVD), including the treatment effects with rivaroxaban or warfarin.
Methods and results: Cox regression was used to adjust comparisons for potential confounders. Of 14,264 pts included in the trial, 215 had diagnosis of AS (n=215), 12,179 had no SVD. AS pts were older (78 vs. 72 years), heavier (BMI 29 vs. 28 kg/m^2), had similar rates of persistent AF (80% vs. 81%), more peripheral artery disease (15% vs. 6%) and prior MI (30% vs. 16%), and had a slightly higher CHADS2 score (3.6 vs. 3.5) than pts without SVD. Independent of treatment allocation, efficacy outcomes in AS pts occurred approximately twice as often as in pts without SVD (Table). Bleeding events were also more frequent in pts with AS. When comparing rivaroxaban and warfarin groups, treatment effects were consistent across AS and no-SVD groups for all endpoints.

Table 1. Efficacy and safety endpoints for AS and no-SVD patients

	Events/100 pt-yrs (total events)		AS vs. no SVD Adjusted HR (CI)
	AS	No SVD	
Efficacy outcomes			
Stroke or systemic embolism (SE)	4.21 (17)	2.09 (487)	1.82 (1.10, 3.01)
Stroke, SE, or vascular death	10.84 (41)	4.31 (982)	2.03 (1.47, 2.79)
Stroke, SE, vascular death, or MI	12.09 (45)	4.99 (1128)	1.91 (1.41, 2.59)
Stroke	3.68 (15)	1.96 (458)	1.70 (1.00, 2.92)
All-cause death	11.22 (43)	4.39 (1002)	1.88 (1.38, 2.56)
Safety outcomes			
Major or NMCR bleeding	24.36 (59)	14.16 (2431)	1.28 (0.98, 1.66)
Major bleeding	7.61 (21)	3.27 (625)	1.61 (1.03, 2.49)
Intracranial hemorrhage	1.40 (4)	0.59 (114)	2.04 (0.75, 5.60)

Conclusions: Pts with AS and AF have significantly more frequent ischemic and bleeding events than pts without SVD. Given the small numbers of pts and events in AS group, conclusions regarding treatment effects need to be drawn with caution. This is the first study suggesting that efficacy and safety outcomes of pts with aortic stenosis on oral anticoagulation are distinctly different from pts without SVD.

5836 | BEDSIDE

All-cause mortality risk over time in men and women with incident atrial fibrillation - a Swedish nation-wide registry analysis

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Purpose: Atrial fibrillation (AF) is frequently associated with increased morbidity and mortality. We analyzed mortality trends over time in a nation-wide AF patient population and hypothesized that patients with incident AF as the primary diagnosis would have a lower risk than those with AF as a secondary diagnosis.
Methods: 272186 patients, aged <65 years (21%), 65-74 years (27%) and 75-85 years (52%), were hospitalized with incident AF between 1995 and 2008. Patients were divided into two groups, those with AF as their primary diagnosis and those with AF as a secondary diagnosis. Each patient was age and gender matched with 1-2 persons free of AF, altogether 544344 controls. Patients and controls were followed via record linkage with the Swedish National Patient and Cause of Death Registries.
Results: In all, 119 631 (45% women) and 152 555 (43% women) patients were identified with incidental AF as primary and secondary diagnoses, respectively. In the whole study population, the relative risk of mortality versus controls was highest during the first year after diagnosis in all age categories. In women the risk was 7.67, 4.44 and 2.81 ($p<0.001$) in the age categories <65, 65-74 and 75-85 years, respectively, and the corresponding figures in men were 4.99, 3.13 and 2.33 ($p<0.001$). The risk versus controls declined significantly over time, at 1-2 years to 4.03, 2.82 and 1.99 ($p<0.001$) among women and 3.62, 2.29 and 1.70 ($p<0.001$) among men, and at 2-5 years to 3.04, 2.29 and 1.83 ($p<0.001$) in women and 2.58, 1.89 and 1.58 ($p<0.001$) in men. The relative and absolute risks of mortality were consistently lower in patients with AF as the primary than as a secondary diagnosis.
Conclusion: The relative mortality risk over time was higher in women than in men. The patients were at the highest relative risk of mortality during the first year after diagnosis. The mortality risk over time was consistently lower in patients with a primary than a secondary AF diagnosis.

GENETIC ASPECTS OF ARRHYTHMIAS

P5837 | BEDSIDE

Prevalence of children and adolescents with long QT syndrome (LQTS) according to the criteria of the HRS/EHRA/APHRS Expert Consensus Statement

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Background: A school-based electrocardiographic screening program has been developed for 1st (6 years old), 7th (12 years old), and 10th (15 years old) graders since 1994. The prevalence of LQTS was reported as around 1:1200 in adolescents aged 12 years old, and as around 1:2,000 in apparently healthy live births. Prevalence of LQTS in 6 years olds is unclear and that in 6 and 12 years olds according to the HRS/EHRA/APHRS criteria is not known.
Subjects and methods: Subjects were 27,348 and 28,869 subjects aged 6 and 12 years old, respectively, who participated in the screening program from 1999 and 2003. The criteria of the statement for the diagnosis of LQTS are (a) the presence of a new LQTS score ≥3.5, and/or (b) the presence of unequivocally pathogenic mutations, or (c) the presence of a QTc ≥500 ms in repeated 12-lead ECGs. Subjects with a secondary cause were excluded. Genetic testing was performed when agreement from their parents was obtained.

Results: Numbers of subjects who fulfilled the criteria were 9 (M/F=5/4) (1:3,039) and 23 (M/F=11/12) (1:1,255) in 6- and 12-year-old subjects, respectively. Genetic testing was performed in 8 subjects and mutation was determined in 4 subjects. All but one fulfilled the LQTS score criteria {criteria (a)}. A 6-year-old girl had a score of 3 and a radical mutation (G745 fs+54X) in KCNH2.
Conclusion: Prevalence of LQTS in 6- and 12-year-old subjects was about 1:3,000 and 1:1,250, respectively. Prevalence in 12 years olds was similar to the former report. The new LQTS scoring system is useful for clinical diagnosis of LQTS in both children and adolescents. These data may be a reference for the ECG screening programs.

P5838 | BENCH
A novel cardiac alpha-myosin heavy chain (MYH6) mutation impairing sarcomere structure responsible for familial sick sinus syndrome

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Purpose: Sick sinus syndrome (SSS) is a common arrhythmia often associated with aging or underlying structural heart diseases, but it may occur in a familial form. Mutations responsible for familial SSS have been demonstrated in several genes including SCN5A and HCN4, and recent genome-wide association studies have shown a rare variation (R721W) of the α-myosin heavy chain (α-MHC) gene MYH6 increasing susceptibility to SSS. α-MHC is a sarcomeric protein predominantly expressed in the atrium, and its knockdown animals showed impaired sarcomere structures and defective atrial contraction. Our goal was to identify genetic defects of MYH6 in familial SSS and elucidate the molecular pathophysiology underlying SSS with MYH6 mutations.
Methods: We genetically screened MYH6 in nine genotype-negative SSS families using PCR direct sequencing strategy. Since the mutations in MYH6 are linked to cardiomyopathy and a variety of congenital heart diseases and known to impair the myofibril formation, we assessed the morphological changes of sarcomere attributable to the MYH6 mutations.
Results: Frame 3bp deletion mutation delE933 (c.2797_2799delGAG) was identified in the exon 22 of MYH6 in a 62 year-old female who had a pacemaker implanted with a diagnosis of SSS. Her deceased mother also had a pacemaker implanted due to SSS. The delE933 was not identified in 400 healthy Japanese control subjects as well as in 1000 Genomes database or dbSNP. Echocardiography showed mild dilatation of left ventricle and right atrium, but there was no sign of cardiomyopathy, congenital heart diseases, or cardiac dysfunction. Immunofluorescent imaging of neonatal rat cardiomyocytes transfected with MYH6-R721W and delE933 showed brightly fluorescent speckles of α-MHC and lack of organized repeating units characteristics of myofibrils, demonstrating markedly impaired sacromeric structural integrity. The residue E933 of MYH6 is located at the highly conserved region across different species for both α- and β-MHC isoforms. Co-immunoprecipitation study revealed that the delE933 α-MHC resulted in enhancing binding affinity to myosin binding protein-C. Since MYH6 is predominantly expressed in the atrium, it is suggested the variations or mutations of MYH6 may disrupt the sarcomeric integrity of the atrial muscle surrounding sinus node, which in turn progresses to manifest sinus node dysfunction.
Conclusion: We propose a new disease entity of inherited arrhythmias attributable to mutations in genes encoding sarcomere proteins other than cardiac ion channels or ion channel-associated genes.

P5839 | BEDSIDE
Genetic modifiers in the long QT3/Brugada overlap-syndrome caused by E1784K

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Purpose: Long QT syndrome (LQTS) and Brugada syndrome (BrS) are genetic arrhythmia disorders characterised by sudden death and highly variable penetrance. The E1784K mutation in SCN5A, the α-subunit of Nav1.5, causes a LQT3/BrS overlap disease and is the most commonly identified mutation in LQT3 and BrS. The aim of this project is to identify genetic modifiers of the variable phenotype in an international cohort of E1784K carriers. Identification of genetic modifiers will increase our understanding of pathophysiology and may improve risk stratification.
Methods: We genotyped 88 caucasian E1784K mutation carriers from 14 families for 48 single nucleotide polymorphisms (SNPs) previously shown to be modifiers of different electrocardiographic (ECG) traits in the general population in large genome wide association studies. Association with PR interval, QRS duration, QTc interval, Brugada phenotype and time to occurrence of symptoms was tested using the R-package coxme (mixed effects Cox-models) with adjustment for age and sex. P-values are uncorrected for multiple testing.
Results: Eight SNPs showed significant association ($p<0.05$) with PR interval with effect sizes (change per minor allele) of -21.7 to +15.5 ms. Two SNPs were significantly ($p<0.05$) and one SNP was highly significantly (p=0.0022, rs251253, Chr 5) associated with QRS duration with effect sizes between -5.9 and +8.2 ms. Three SNPs showed association with QTc duration ($p<0.05$) with effect sizes of +11.9 to +13.4 ms. Four SNPs were significantly and five SNPs highly significantly ($p<0.005$) associated with the presence of the Brugada phenotype. Two SNPs (rs11047543, Chr 12 and rs17020136, Chr 2) were associated with the occurrence of symptoms (cardiac syncope, ventricular tachycardia, aborted cardiac arrest) with p-values of 0.0467 and 0.0154 and odds ratios of 3.35 and 2.61 respectively.
Conclusion: Several SNPs showed significant and highly significant association with different ECG traits and occurrence of symptoms in this cohort of E1784K carriers with a LQT3/BrS overlap disease. These results will require replication in additional cohorts, other ethnic groups and patient groups with LQT3 and Brugada syndrome. Functional studies will need to provide supporting evidence for the modifier function of highlighted genes and variants. However, these results provide promising initial evidence for the role of genetic modifiers in the phenotypic variation of LQT3 and BrS.

P5840 | BEDSIDE
Genetic markers of arrhythmia risk following acute coronary syndromes

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Background: Survivors of acute coronary syndromes (ACS) are at risk of ventricular arrhythmias, with a genetic component indicated both directly & in markers of arrhythmia such as the QT interval. We investigated single nucleotide polymorphisms (SNPs) previously associated with the QT interval or arrhythmia for association with prolonged repolarisation & with sudden cardiac death/cardiac arrest (SCD/CA) in patients hospitalised for ACS.
Methods: Patients with ACS were enrolled in the prospective Coronary Disease Cohort Study & followed for clinical events for a median of 5.0 years (IQR 3.6, 6.8). Clinical, echo & neurohormonal data were collected for 12 months. 33 SNPs were genotyped & tested for univariate associations with time to SCD/CA, & with prolonged repolarisation (QTc interval >440ms, or if ECG LBBB & QRS duration >120ms, a JTc interval >370ms). After correction for multiple testing (false discovery rate), significant SNPs were tested in multivariable (MV) Cox or logistic regression models with pre-specified clinical predictors to determine whether the SNP provided additional prognostic information (using an additive genetic model).
Results: 1657 Caucasian patients were included (104 SCD/CA events). Patients with SCD/CA were older (70 vs 67 years), were more likely to have diabetes, prior ACS & heart failure, renal dysfunction & LBBB on admission ECG than those without events. Four SNPs had significant univariate associations with SCD /CA following correction for multiple testing: rs10919071 (ATP1B1), rs17779747 (KCNJ2), rs3864180 (GPC5), & rs876188 (C14orf64). In a MV model with variables available at admission rs17779747, rs3864180, & rs876188 were significantly associated with SCD/CA; rs17779747 with a decreased risk (HR = 0.66, 95% CI 0.48, 0.90, p=0.0008), & rs3864180 & rs876188 with an increased risk. Three SNPs were significantly associated with prolonged repolarisation at 12 months: rs10494366 and rs12143842 (NOS1AP), & rs7132154 (CACNA1C). In a MV model with 12 month visit data (age, gender, NT-proBNP, LV end systolic volume, diabetes and LBBB) rs10494366 remained a significant predictor. No SNPs were significantly associated with prolonged repolarisation on the acute admission ECGs.
Conclusions: Three SNPs were associated with SCD/CA in patients following ACS, after adjustment for clinical covariates. Polymorphisms of the NOS1AP gene were associated with prolonged repolarisation 12 months post ACS, but not during the acute phase where the clinical predictors associated with the acute event dominated the model.

P5841 | BENCH
Genetic variants on chromosome 4q25 associated with atrial fibrillation upregulate PITX2 expression

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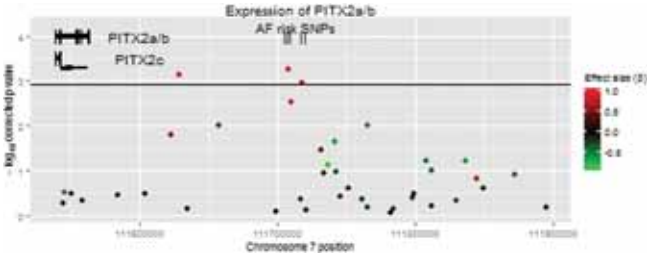
Purpose: Genome-wide association studies (GWAS) have identified a strong as-

sociation between atrial fibrillation (AF) and genetic variants in chromosome 4q25 which lie 120 kilobases from the nearest gene, PITX2 which has 3 known isoforms. PITX2c, which establishes the cardiac left-right axis, and PITX2a and b, which share a promoter and have unknown roles in cardiac development. In order to investigate the mechanism of this association we mapped associations between single nucleotide polymorphisms (SNPs) and expression of PITX2 in human atrial tissue.
Methods: 122 right atrial appendage (RAA) and 12 left atrial appendage (LAA) samples were collected from patients undergoing cardiac surgery. 22 RAA samples and 6 LAA samples were from patients with a history of AF. In order to tag genetic variation at the 4q25 locus, 42 SNPs were genotyped using the Sequenom platform. Expression of transcripts PITX2a/b and PITX2c were measured using TaqMan assays and normalised to three reference genes.
Results: The risk alleles of 3 variants associated with AF were associated with increased expression of PITX2a/b in RAA. rs17042171-A was associated with a 2.01-fold increase (p=5.34e-04), rs2200733 with a 1.95-fold increase (p=3.06e-03), and rs6843082 with a 1.79-fold increase (p=1.13e-03). PITX2c expression was not associated with the risk SNPs. PITX2a/b expression was 3.32-fold greater in LAA vs. RAA (p=5.55e-07), and PITX2c expression was 102-fold greater in LAA vs. RAA (p=3.20e-12).



Conclusions: Risk variants for AF are associated with markedly increased expression of PITX2a/b. This provides evidence for the overexpression of PITX2a/b as the underlying mechanism of the AF risk variants at this locus.

P5842 | BENCH
Functional characterization of rare variants associated with lone atrial fibrillation

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Background: Mutations in multiple genes were implicated in lone atrial fibrillation (AF) in which abnormally-functioning mutants may cause ectopic activity or action potential duration shortening. However, few data exist regarding functional characterization of these mutations to identify a causal relationship between a gene variant and occurrence of AF.
Objective: We sought to determine the frequency of 12 AF-associated genes in patients with lone AF and characterized the electrophysiological properties of the detected mutations.
Methods and results: We studied 90 patients with lone AF whose onset was 47±11 years old (66 men, mean age 56±13 years). Lone AF was defined as AF occurring at age <65 years without hypertension, overt structural heart disease, myocardial infarction, congestive heart failure, or thyroid dysfunction. There were 26 (29%) with familial AF and 33 (37%) with chronic AF. In these patients, we screened for variants in all exons of KCNQ1, KCNH2, KCNE1, KCNE2, KCNJ2 KCNA5, SCN5A, SCN1B, SCN2B, SCN3B, GJA5 and NPPA by high-resolution melting curve analysis and automated bidirectional DNA sequencing. Rare variants were defined as variants with a reported minor allele frequency (MAF) <0.1% in the NHLBI Exome Sequencing Project Exome Variant Server. The potassium and sodium currents were analyzed using whole-cell patch clamp technique. Among 90 patients with lone AF, we identified 7 rare variants in 8 patients: KCNQ1 1462-1463 ins ACCTGG, KCNH2 T436M, KCNH2 T895M, KCNA5 H463R, KCNA5 T527M, SCN5A R986Q and SCN1B T189M. The probands with both KCNH2 mutations had a family history of AF, and those with the other mutations and variants did not. Electrophysiological study showed that the current densities of both KCNH2 mutations were significantly bigger than that of WT. Both slow and fast time constants in T436M KCNH2 channel increased significantly. In contrast, KCNA5 H463R mutant generated no current at all having with dominant negative suppression. KCNA5 T527M was found to be a loss-of-function mutation responsible for AF. Interestingly, SCN5A R986Q mutant reduced sodium current, and SCN1B T189M mutant increased SCN5A-mediated current with a negative shift in the voltage dependence of activation.
Conclusions: In our cohort of lone AF patients, 7 rare variants in cardiac ion channels were identified in 8 probands with a prevalence of approximately 9%. Functional study suggests that these gene variants may predispose patients without underlying heart disease to AF, providing new insights into the molecular etiology involved in the pathogenesis of AF.

P5843 | BENCH
PITX2c gain-of-function mutation associated with atrial fibrillation

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Purpose: Genome-wide association studies have associated a genetic variant (rs2200733) located upstream of PITX2c with atrial fibrillation (AF), suggesting a potential role of PITX2c in AF. This study aimed to identify rare variants in PITX2c predisposing to AF.
Methods: The coding region of PITX2c was Sanger sequenced in two independent AF cohorts.
Results: The p.Met207Val variant was identified in 5 patients in a European cohort of 402 patients with early-onset lone AF, but not in any of the 810 controls matched on ethnicity. The frequency of p.Met207Val was significantly higher in patients vs. 7031 controls (0.62% vs. 0.02%, OR=29.3 95%, CI: 5.7 - 189.1, p=0.00002). The associations was replicated in a independent cohort of 462 European American early-onset AF cases and 4760 controls (P=0.018). A pool analyzes that included all 864 early-onset AF patients and all 11791 controls indicated a OR of 15,5 (0.46% vs. 0.03%, OR=15.7, 95%, CI: 5,0 - 50.8, p=1.9 x 10 -06). Reporter gene assays, electrophoretic mobility shift assay, Western blot, mRNA expression analyses, and allele frequency evaluation were performed to characterize the identified variant. p.Met207Val variants were associated with increased transactivational activity of PITX2c and increased mRNAs of KCNQ1, KCNH2, SCN1B, GJA5 and GJA1.
Conclusions: We report a genetic association between the variant p.Met207Val and early onset AF, which is also replicated in an independent cohort. A pool analyzes that included all 864 early-onset AF patients and all 11791 controls indicated a OR of 15,5 (p=1.9 x 10 -06) This rare variant seems to be causing gain-of-function in PITX2c transactivation activity and in expression of genes related to AF.

DEFINING PROGNOSIS IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

P5844 | BEDSIDE
Incidence, determinants and prognosis of heart failure with normal ejection fraction in patients admitted for myocardial infarction; data from 91.360 patients in the SWEDEHEART registry

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Aim: To analyze the incidence and predictors of heart failure with normal EF (HFNEF) and its effect on outcome in acute myocardial infarction (AMI).
Design, setting and participants: The nationwide registry SWEDEHEART records baseline characteristics, treatments and outcome in consecutive patients with AMI admitted to all coronary care units in Sweden. In-hospital heart failure (HF) was defined as presence of crackles at admission (Killip class >1), or use of iv diuretics, or use of iv inotropic drugs during hospitalization. Reduced EF (REF) was defined as EF <50%, HFREF if there is HF with REF and NEF as ≥50% with out HF. All patients in the registry with AMI between 1998-2010 and an available EF were included in the analysis (n=91.360).
Results: Among patients with HF, the proportion of HFNEF showed a relative increase (18 to 31%). The incidence of HFNEF in the total AMI population remained fairly unchanged (7.7 to 8.1%). The proportion of patients with HFREF declined dramatically (47 to 26%) as did the proportion of REF patients without HF (20 to 16%). AMI patients discharged with NEF without HF increased (25 to 50%). Age, female gender, diabetes, hypertension and renal failure were strong predictors of HFNEF. Patients who developed HFNEF had considerably higher mortality compared to patients without HF irrespective of EF. (HR and 95% CI: REF without HF (1.6 [1.5-1.65]), HFNEF (3.3 [3.1-3.4]) and HFREF (4.5 [4.4-4.6]) compared to patients with no HF and NEF, Fig 1).

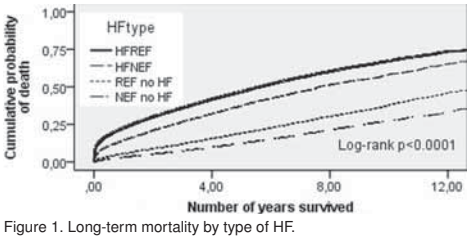

Figure 1. Long-term mortality by type of HF.

Conclusion: The proportion of AMI patients with HFNEF is unchanged over the years in contrast to a dramatic decline in the proportion of HFREF. Patients with

HFNEF have considerably worse prognosis compared to patients without HF regardless of EF. Clinical findings of HF are important to risk stratify patients after AMI.

P5845 | BEDSIDE
Prognostic impact of diastolic dysfunction in patients with heart failure with reduced ejection fraction: a cross-sectional analysis from the German Competence Network Heart Failure

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Background and purpose: In patients with heart failure with reduced ejection fraction (HFrEF), the presence of either systolic or diastolic left ventricular dysfunction is a well-acknowledged sign of an unfavourable prognosis. However, the detailed interaction of diastolic and systolic dysfunction (DD, SD) and its prognostic importance has not been systematically investigated so far.
Methods: From the German Competence Network Heart Failure, 1046 patients with HFrEF were analysed. Patients were grouped according to severity of left ventricular systolic dysfunction (SD: ejection fraction 35-50% (mSD) vs. ejection fraction <35% (sSD)) and diastolic dysfunction (DD: E/E'<15 (mDD) vs. E/E'>15 (sDD)). Cumulative incidences of death and hospitalisation, mean time to hospitalisation or death, number of hospitalisations and length of hospital stay were studied during a median follow-up time of 5 years. Age-adjusted Cox regression was used to examine the prognostic utility.
Results: In patients with mSD (52.5% of the cohort), additional presence of sDD was associated with an absolute increase in overall mortality risk from 16.9% to 26.0% (p=0.004). Vice versa, in patients with mDD, additional sSD was associated with a risk increase from 16.9% to 34.0% (p<0.001). However, in patients with sSD, additional sDD hardly affected mortality risk (34.0 vs. 34.5%). With respect to cardiovascular death, similar results were demonstrated. Further, worse systolic function predicted endpoints as cardiovascular hospitalisation or cardiac death, numbers of hospitalisations, and length of hospital stay. Solely in patients with mSD mean time to cardiovascular hospitalisation or cardiac death showed a significant association with worsening diastolic function (p=0.017).
Conclusions: In patients with HFrEF, the evaluation of both, diastolic and systolic function, provides additional prognostic information. The degree of DD and its impact as a prognostic marker seems to be of higher relevance in patients with mild-to-moderate SD.

P5846 | BEDSIDE
Outcome in heart failure with preserved ejection fraction strongly depends on right ventricular performance

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Background: Heart failure with preserved ejection fraction (HFpEF) is recognized as a major cause of cardiovascular morbidity and mortality. However, knowledge of risk factors in this specific patient population is scarce. Therefore, we aimed to improve risk prediction using a large variety of imaging modalities including hemodynamic, echocardiography and cardiac magnetic resonance (CMR) imaging.
Methods: We prospectively included 142 patients with a definite diagnosis of HFpEF into our observational registry. Echocardiography, CMR and invasive hemodynamic assessments were performed in all patients. Hospitalization for heart failure and/or cardiac death as primary outcome was observed over a median follow up of 10 months.
Results: We did not detect a significant association between imaging or functional parameters of the left ventricle and outcome in our adjusted analysis. However, the strongest risk factors were reduced right ventricular function measured using echocardiography (adj. HR 6.53; 95% CI 3.08-13.83; P<0.001) or CMR (adj. HR 6.67; 95% CI 1.82-24.48; P=0.004) and systolic pulmonary arterial pressure using echocardiography (adj. HR per 1-SD 1.46; 95% CI 1.07-2.00; P=0.02) and invasive measurements (adj. HR per 1-SD 1.55; 95% CI 1.15-2.09; P=0.004). Kaplan Meier analysis demonstrated a significant increase of the primary endpoint in patients with significantly reduced right ventricular function (Fig. 1A; P<0.001), in patients with increased systolic pulmonary arterial pressure (Fig. 1B; P=0.001).
Conclusion: Outcome in patients with HFpEF does not correlate with left ventricular size or function but strongly depends on the performance of the right ventricle. For optimal clinical management thorough evaluation of the right ventricle is indispensable in affected patients.

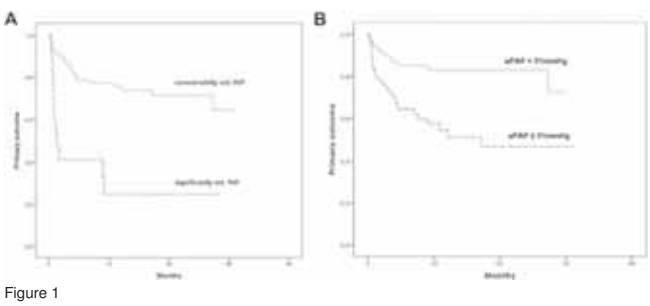

Figure 1

P5847 | BEDSIDE
High prevalence of elevated high sensitivity troponin-T and reduction in levels by LCZ696 in heart failure with preserved ejection fraction in the PARAMOUNT trial

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Background: Elevation of high sensitivity troponin T (hs-TnT) has been shown to have prognostic significance in heart failure with reduced ejection fraction (HFrEF) but its significance in heart failure with preserved ejection fraction (HFpEF) is unclear.
Methods: We studied 298 patients from the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) trial randomized to the angiotensin receptor neprilysin inhibitor LCZ696 or valsartan. We related troponin concentration to baseline clinical and echocardiographic measures and assessed the effect of randomized therapy on hsTn-T levels at 12 and 36 weeks.
Results: hsTn-T was elevated (>0.014 μg/L) in 55% of patients, and was associated with older age, a history of diabetes, higher NT-proBNP, lower eGFR, greater ventricular volumes and LV mass (Table). Treatment with LCZ696 led to a 12% reduction in hs-TnT at 12 weeks (p=0.05) and a 14% reduction at 36 weeks (p=0.03) compared with valsartan.

Characteristics by hs-TnT in HFpEF

	hs-TnT ≤0.014 μg/L N=134 (45%)	hs-TnT >0.014μg/L N=164 (55%)	P
Age	70 (9)	72 (9)	0.01
History of diabetes	40 (30%)	74 (45%)	0.01
NT-proBNP (pg/mL)	684 (376–999)	1145 (652–2067)	<0.001
eGFR (mL/min per 1.73 m^2)	72 (21)	60 (18)	<0.001
Beta-blockers	113 (84%)	122 (74%)	0.04
LA diameter (cm)	3.6 (0.4)	3.8 (0.5)	<0.05
LV end diastolic volume (mL)	109 (30)	117 (28)	0.04
LV mass (g)	136 (33)	158 (47)	<0.001

LA, left atrial; LV, left ventricular; eGFR, estimated glomerular filtration rate.

Conclusion: Elevated hs-TnT is prevalent in HFpEF and is associated with other markers of disease severity. Neprilysin inhibition was associated with reduction in hs-TnT.

P5848 | BEDSIDE
References values for left ventricular diastolic function parameters: results from the NORRE study

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Purpose: Pulse Doppler and Tissue Doppler imaging (TDI) parameters have a fundamental role in the diagnosis of diastolic dysfunction. However, current guidelines do not take into account the possible differences related to age and gender. In this study, we reported gender and age specific differences in diastolic parameters in normal subjects.
Methods: The NORRE study is a multi-centre study investigating echocardiographic parameters in a large cohort of healthy population (n=734; 45.8±13.3years; 43.6% of male). E and A waves and isovolumic relaxation time (IVRT) were measured. Mitral e' and a' wave velocities and IVRT were obtained from TDI at septal, lateral, inferior, anterior and posterior mitral annulus. Doppler parameters were analyzed according to gender and age (20-40; 40-60; >60 years).
Results: Higher E wave was obtained in females (74.1 vs. 82.2cm/s). No differences were found regarding A wave, E/A ratio and IVRT according to gender. Older patients showed a significantly lower E wave, E/A ratio, a higher A wave and longer IVRT. Regarding TDI parameters, there were no significant differences according to gender, except higher a' wave in males (10.4 vs. 9.2cm/s). Older patients showed significant lower e', higher a' wave (8.7 vs. 10.1vs. 11.3cm/s) and longer IVRT in all the walls. There was a strong correlation between age and e'

Table 1

Parameters	20–40 years	40–60 years	>60 years	All	r	p-value
E (cm/s)	83.9±17.5	77.6±16.1	67.6±16.4	78.8±17.6	–0.34	<0.001
Septal e' (cm/s)	13.0±2.5	10.8±3.0	8.1±2.4	11.4±3.2	–0.56	<0.001
Lateral e' (cm/s)	17.6±3.6	13.3±3.1	9.5±2.2	14.6±4.4	–0.69	<0.001
Inferior e' (cm/s)	14.8±3.1	12.4±3.5	8.4±1.9	13.0±3.8	–0.66	<0.001
Anterior e' (cm/s)	15.6±2.7	12.1±3.0	8.7±2.2	13.4±3.7	–0.72	<0.001
Posterior e' (cm/s)	17.2±2.7	13.4±3.3	10.0±2.6	14.8±4.0	–0.76	<0.001
E/e' septal	6.6±1.8	7.6±2.1	8.8±2.6	7.3±2.2	0.36	<0.001
E/e' lateral	5.0±1.6	6.1±1.7	7.7±2.7	5.8±2.0	0.44	<0.001
E/e' (septal + lateral)	5.6±1.6	6.7±1.7	8.1±2.4	6.4±2.0	0.43	<0.001

and a' wave (r=0.49, p<0.001). E/e' ratio was also significantly higher in older patients.

Conclusions: Diastolic parameters are strongly influenced by age. This should be taken into account using individual parameters according to age categories in the evaluation of diastolic function.

P5849 | BEDSIDE

Which is better for improving diastolic function in patients with hypertension and left ventricular diastolic dysfunction, thiazide/ARB or CCB/ARB? Results of multicenter randomized trial

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Background: Hypertension is associated with an increased risk of diastolic dysfunction. In our previous studies, we demonstrated that reduction of blood pressure by a calcium channel blocker (CCB) or adding hydrochlorothiazide (HCTZ) to an angiotensin receptor blocker (ARB) is associated with improvement in left ventricular (LV) diastolic function in patients with hypertension and diastolic dysfunction. It remains unknown which combination is better to improve LV diastolic function, HCTZ/ARB or CCB/ARB. We conducted multicenter trial to compare the effects of HCTZ and CCB when used in combination with an ARB on LV diastolic function.

Methods: We enrolled 297 hypertensive patients with diastolic dysfunction from 31 sites. Patients received ARB monotherapy for at least 8 weeks, followed by additional use of HCTZ (n=149) or amlodipine (n=148) for 24 weeks after randomization. Primary end point is change in early diastolic mitral annular velocity (e'). We also measured the ratio of mitral inflow velocity to e' velocity (E/e' ratio) and brain natriuretic peptide (BNP).

Results: Blood pressure (BP) decreased from baseline to 24-week later in both groups (157/90 vs. 134/78 mmHg (P<0.001) in HCTZ/ARB, 156/88 vs. 130/75 mmHg (P<0.001) in CCB/ARB). There were no differences in magnitude of BP reduction and 24-week BP between both groups. The e' velocity increased from 5.9 to 6.4 cm/s (Δ 0.5; P<0.001) in HCTZ/ARB and from 5.6 to 6.2 cm/s (Δ0.6; P<0.001) in CCB/ARB. There was no difference in change in e' velocity and 24-week e' velocity both groups between the 2 groups. E/e' and log BNP significantly improved only in HCTZ/ARB (E/e': 11.4 vs. 10.2; log BNP: 3.18 vs. 2.97, all P<0.001).

Conclusions: Both adding HCTZ or CCB to ARB are associated with improvement in LV relaxation (increase in e' velocity). The combination of ARB and HCTZ may have a more beneficial effect on LV filling pressure (decrease in E/e' ratio and BNP).

P5850 | BEDSIDE

Comparison of the echocardiographic definition of left ventricular diastolic dysfunction using the 2007 ESC and the 2009 EAE/ASE recommendations in metabolic syndrome patients

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Purpose: Identifying patients at risk for diastolic dysfunction (DD) may help prevent the occurrence of heart failure with normal ejection fraction (HFNEF), which is associated with high morbidity and mortality. Currently there is no consensus on how to define DD. We compared clinical predictors of DD and diagnostic accuracy of DD in patients with metabolic syndrome (MetS) using the 2007 European consensus statement and the 2009 EAE/ASE recommendation.

Methods: The Metabolic risk-diastolic heart failure (METR-DHF) is a cross-sectional cohort of 496 subjects with MetS (NCEPIII criteria) and normal left ventricular (LV) systolic function - EF >50% and LV end-diastolic volume index <97 ml/m^2. Diastolic dysfunction was defined first, according to the 2007 European consensus statement on the diagnosis of HFNEF as: possible DD (E/E'≥8) and definite DD (E/E'>15 or E/E' 8-15 + additional specified ECHO criteria, such as LV mass index >122 for women/ >149 ml/m^2 for men), and secondly, according to the 2009 European EAE/ASE recommendation as: Septal E'<8 or Lateral E'<10 or Left atrial volume (LA ≥34 ml/m^2), with severity grading (grade 1, 2 or 3) according to other specified ECHO criteria. Multivariate binary logistic regression and ROC curves were used to assess clinical predictors of DD and diagnostic accuracy of DD.

Results: According to the 2007 ESC consensus, 231 (47%) patients had possible DD and 89 (18%) had definite DD. According to the 2009 EAE/ASE recommendation, 341 (69%) patients had DD, with 177 (36%) having mild, 160 (32%) moderate, and 4 (1%) severe dysfunction. Using the 2007 ESC consensus, multivariable analysis using either the criteria of possible or definite DD showed that older age, female sex, higher body mass index, history of hypertension and prescription of beta blockers were associated with a higher risk of DD. In addition, elevated heart rate and prescription of digoxin were associated with definite DD. Using the 2009 EAE/ASE recommendation only older age and non-prescription of digoxin were associated with a higher risk of DD. The C statistic was 0.79 (CI 0.75-0.83) for the 2007 ESC consensus, and 0.71 (CI 0.66-0.76) for the 2009 EAE/ASE recommendation.

Conclusions: In patients with MetS, only the use of the 2007 ESC consensus identified DD to be associated with MetS related risk factors. Furthermore, diagnostic accuracy of DD was higher for the 2007 ESC consensus than for the 2009 EAE/ASE recommendation. Future efforts to improve the diagnosis of DD with novel biomarkers should demonstrate accuracy superior to the 2007 ESC consensus.

NEWS FROM THE AORTIC VALVE

P5851 | BEDSIDE

Impact of periprocedural stroke on mid-term mortality after transcatheter aortic valve implantation

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Purpose: Stroke occurrence in patients undergoing transcatheter aortic valve implantation (TAVI) has been reported among complications in several studies. The aim of this study was to assess the impact of periprocedural stroke on mortality at mid-term follow-up after TAVI.

Methods: Six-hundred-fifty-six patients with aortic stenosis underwent TAVI with the CoreValve system (92.8%) or the Edwards SAPIEN valve system (7.2%). Stroke and transient ischemic attack were defined according to the Valve Academic Research Consortium-2 consensus document. A cerebrovascular accident (CVA) was defined as any stroke or transient ischemic attack. Periprocedural stroke or CVA were defined as stroke or CVA occurring within 72 hours from the index procedure. Separate multivariable Cox regression analyses were performed to calculate hazard ratio (HR) with 95% confidence intervals (CI) of mortality for periprocedural stroke and periprocedural CVA, respectively.

Results: Procedural success occurred in 97.4% of patients. The incidence of any stroke and of CVA after the index procedure was 2.4% and 2.7%, respectively. Periprocedural strokes accounted for 56.2% of all strokes and occurred in 1.4% of patients included in the study. Periprocedural CVA accounted for 55.6% of all CVA and occurred in 1.5% of patients. After a median follow-up of 434 days, all-cause mortality was significantly higher in patients with periprocedural stroke as compared to those without (66.7% vs 22.9%, logrank p=0.001), and in patients with periprocedural CVA as compared to those without (70.0% vs 22.8%, logrank p<0.001). At multivariable Cox regression, periprocedural stroke (HR 4.66, 95% CI 1.95-11.1, p=0.001) and periprocedural CVA (HR 4.64, 95% CI 2.06-10.5, p<0.001) were significant predictors of all-cause mortality.

Conclusions: More than half of strokes and CVA following TAVI occur within the periprocedural period. Periprocedural stroke and CVA are independent predictors of all-cause mortality at mid-term follow-up. Strategies for periprocedural cerebrovascular events prevention are needed.

P5852 | BEDSIDE

Impact of aortic annulus size on valve hemodynamics and clinical outcomes following transcatheter and surgical aortic valve replacement: insights from the PARTNER trial

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Purpose: The objectives of this study were to evaluate valve hemodynamics and clinical outcomes in those patients included in the PARTNER randomized con-

trolled trial (RCT) cohort A and the PARTNER non-randomized continued access (NRCA) cohort according to aortic annulus size.
Methods: Patients included the RCT (n=574) and NRCA (n=1358) cohorts were divided in tertiles according to aortic annulus diameter (small, medium, large aortic annulus; SAA, MAA and LAA, respectively) as measured by transthoracic echocardiography. Moderate-to-severe prosthesis-patient mismatch (PPM) was defined as an effective aortic orifice area of $\leq$0.85 cm^2/m^2.
Results: In the RCT, patients who had TAVR in the SAA group had a lower incidence of PPM (39% vs. 63%, P=0.01) with only a mild increase in moderate-to-severe paravalvular leaks (PL) compared to SAVR (5.7% vs. 0%, P=0.06), while no differences in PPM between groups and a significant increase in moderate-to-severe PL associated with TAVR were observed in the LAA group (9% vs. 0%, P=0.01). TAVR was associated with a tendency towards a lower mortality (32.1% vs. 42.5%, P=0.11) and higher stroke (10.2% vs. 1.9%, P=0.02) rates at 2-year follow-up compared to SAVR in the SAA group, and no differences in clinical outcomes between TAVR and SAVR were observed in the MAA and LAA groups. In the NRCA, there were no differences in PPM between the SAA and LAA groups, but a higher rate of moderate-to-severe PL was observed in the LAA group (5.9% vs. 11.5%, P=0.004). Patients in the LAA group had a higher mortality rate at 1-year follow-up compared to the SAA and MAA groups (24.8%, 18.3% and 18.7%, respectively, P=0.02), and differences persisted in multivariable analysis (P=0.048 for LAA vs. MAA, P=0.035 for LAA vs. SAA). No differences in stroke rate were observed between groups in the NRCA cohort (3.9%, 4.6% and 5.5% for SAA, MAA, and LAA, respectively, P=0.60).
Conclusions: Aortic annulus size had a major influence in valve hemodynamics and clinical outcomes following TAVR and SAVR. This study highlights the importance of considering aortic annulus size in the evaluation of high-risk patients who are candidates for AVR, and suggest that TAVR may be the preferred strategy for those with smaller aortic annulus.

P5853 | BEDSIDE
Real-world multicenter prospective registry using the direct flow medical transcatheter aortic valve system for the treatment of severe aortic stenosis: comparison with the DISCOVER Trial

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Aims: To assess the performance of the Direct Flow Medical (DFM) transcatheter aortic valve replacement (TAVI) system in a multicenter, real-world experience and to compare these results with the DISCOVER CE-mark trial findings.
Methods and results: In this multicenter, prospective, real-world experience, 105 high-risk patients (Logistic Euroscore: 24.7±14.7) with severe aortic stenosis were prospectively enrolled and underwent TAVI with DFM prosthesis. No significant differences emerged comparing the baseline risk profile between this real-world experience and the DISCOVER trial. Initial positioning and repositioning led to a final reduction of the initial trans-aortic gradient by 45±15 mmHg with a mean residual gradient of 9±4 mmHg. In 98% of cases there was no or only trivial aortic regurgitation after implantation (Grade 0 or 1). The VARC-2-defined device success was 98% (vs. 91% in the DISCOVER trial; p=0.03). Ten patients (10%) underwent permanent pacemaker implantation due to post-procedural persistent advanced atrio-ventricular block (vs 17% in the DISCOVER trial; p=0.148). In 6% of cases device retrieval was successfully performed during the procedure. At 30 day follow-up, the survival rate was 98% (two deaths), with a patient safety event rate of 89%.
Conclusions: In a multicenter, prospectively enrolled, high-risk patient population with severe aortic stenosis, the DFM retrievable and repositionable prosthesis demonstrated excellent short-term efficacy and safety. Even though majority of centers involved in this real-world experience were not involved in the DISCOVER trial, device success was significantly higher.

P5854 | BEDSIDE
Prognostic value of left ventricular filling pressure in asymptomatic aortic valve stenosis

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Purpose: To assess whether an echocardiographic marker of left ventricular (LV) filling pressure predicts future indication for aortic valve replacement (AVR) in patients with asymptomatic aortic valve stenosis (AS) and preserved left ventricular ejection fraction (LVEF).
Methods: We recruited 104 asymptomatic patients with AS and preserved LVEF (>50%). A baseline research transthoracic echocardiography (TTE) was performed on all patients, and the results were blinded for the treating physician. LV filling pressure was estimated by the ratio between early diastolic mitral inflow and mitral annular velocity (E/é). Outcome was defined as indication for AVR determined by the treating physician or sudden cardiac death (SCD).
Results: The mean (SD) age was 72 (9) years, 32% were women and mean AVA by TTE was 1.02 (0.28) cm^2. The median follow up time was 27 (IQR 20-44) months. Indication for AVR due to onset of symptoms was observed in 43 patients (41%). No SCD was observed. Aortic valve area indexed by body surface area, aortic valve calcification grade 4, global longitudinal strain, E/é, and pro-brain natriuretic peptide were significant univariable predictors of AVR. In a multivariable Cox proportional hazard regression model including age, gender and the above variables only E/é was significantly associated with future indication of AVR (HR: 1.10 (95%CI 1.01 to 1.20), p=0.03). Figure 1 shows a Kaplan-Meier plot of event-free survival based on E/é dichotomized by the median (E/é median=12).

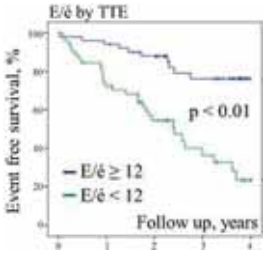

Figure 1. Kaplan-Meier plot E/é.

Conclusion: In the present study E/é is a strong predictor of indication for AVR in patients with asymptomatic AS with preserved LVEF. E/é as a marker of LV filling pressure could be an early marker of subclinical symptom development in asymptomatic AS.

P5855 | BEDSIDE
Increased risk of aortic valve stenosis in patients with psoriasis: a nationwide cohort study

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Purpose: Psoriasis is a chronic inflammatory disease associated with increased risk of cardiovascular disease including atherosclerosis. The pathogenesis of aortic valve stenosis (AS) also includes an inflammatory component. We therefore investigated the risk of AS in patients with psoriasis compared to the general population in a nationwide cohort.
Methods: The study comprised the entire Danish population aged ≥18 years followed from 1st January 1997 until diagnosis of AS, 31st December 2011, or death. Patients with psoriasis and/or AS at baseline were excluded. Information on comorbidity, concomitant medication and socioeconomic status was identified by individual-level linkage of administrative registers. Incidence rates for AS were calculated and hazard ratios (HRs) adjusted for age, gender, comorbidity, medications, and socioeconomic status, were estimated in Cox regression models.
Results: A total of 5,471,422 subjects were eligible for analysis. During the study period we identified 57,175 patients with psoriasis, including 11,669 patients with severe psoriasis. The overall incidence rates for developing AS were 6.13, 12.61, and 16.28 per 10,000 person-years for the reference population (44,959 cases [13.6 mean follow-up years]), mild psoriasis (655 cases [6.6 mean follow-up years]) and severe psoriasis (157 cases [5.6 mean follow-up years]), respectively. Correspondingly, the fully-adjusted HRs for AS were markedly increased in patients with psoriasis with HR 1.25 (95% confidence interval [CI] 1.14–1.38) and HR 1.72 (CI 1.39–2.13) for subjects with mild and severe disease, respectively.
Conclusion: In a nationwide cohort, psoriasis was associated with a disease severity-dependent increased risk of AS. The mechanisms underlying this novel finding require further study.

P5856 | BEDSIDE
Outcome of patients with preserved left ventricular ejection fraction and low gradient severe aortic valve stenosis undergoing aortic valve replacement

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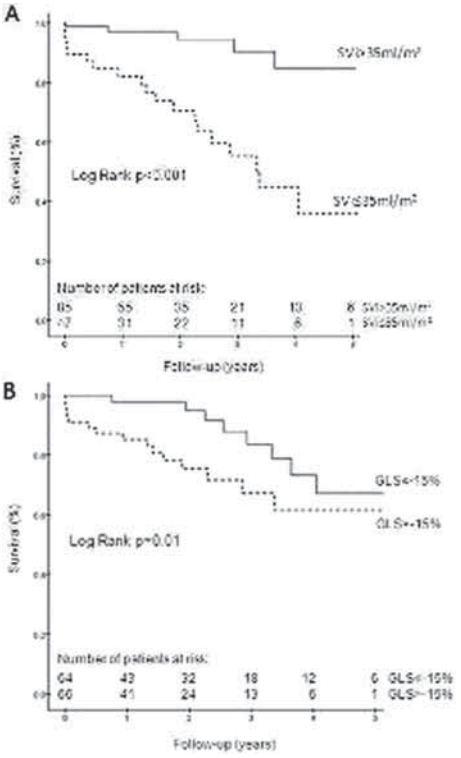
Purpose: The prognostic determinants of patients with severe aortic stenosis (AS) with low gradient preserved ejection fraction (LGprEF) remain unclear. We investigated the relative prognostic merits of flow (measured as stroke volume index [SVi]) and left ventricular (LV) global longitudinal strain (GLS) of patients with severe AS and LGprEF undergoing aortic valve replacement (AVR).
Methods: A total of 134 (75.5±9.9 years, 50% men) patients with severe AS and LGprEF were evaluated. Hemodynamics of aortic valve and LV function were assessed with 2-dimensional, Doppler and speckle tracking echocardiography.

Patients were dichotomized based on SVi (>35ml/m^2 vs. ≤35ml/m^2) and LV GLS (≤-15% vs. >-15%). The end-point was all-cause mortality.
Results: During a median follow-up of 1.8 years (interquartile range 0.5-3), survival was better for patients with SVi >35ml/m^2 and GLS ≤-15% as compared to patients with SVi ≤35ml/m^2 and GLS >-15% (log-rank p=0.01) (Figure). The addition of GLS (X^2 18.00, p=0.02 and C-statistics 0.75) and SVi (X^2 28.62, p<0.001 and C-statistics 0.80) to a baseline model including atrial fibrillation and chronic kidney disease (X^2 12.51, C-statistic 0.69) improved the risk stratification of patients with LGprEF severe AS undergoing AVR.



Kaplan-Meier survival curves post AVR.

Conclusion: SVi and LV GLS are independently associated to survival after AVR in LGprEF severe AS patients.

P5857 | SPOTLIGHT
High-sensitivity Troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic aortic stenosis

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Purpose: High-sensitivity cardiac troponin I (cTnI) assays hold promise in detecting the transition from hypertrophy to heart failure in aortic stenosis. We sought to investigate the mechanism for troponin release in patients with aortic stenosis and whether plasma cTnI concentrations might predict long-term outcome.
Methods: In 122 patients with aortic stenosis (71 [65-77] years, 67% males, and aortic valve area 1.0±0.4 cm^2), left ventricular (LV) mass and myocardial fibrosis (late-gadolinium enhancement (LGE) and T1 mapping) were assessed by 3T cardiac magnetic resonance, and aortic stenosis severity by echocardiography. Aortic valve replacement (AVR) and cardiovascular deaths were adjudicated in 131 patients (69 [62-75] years, 70% males, and aortic valve area 1.1±0.4cm^2) from the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact of REgression (SALTIRE) trial. Baseline plasma cTnI concentrations were measured in all 253 patients using a high-sensitivity assay.
Results: The indexed LV mass and extent of LGE were associated with cTnI concentrations independent of age, sex, coronary artery disease, aortic stenosis severity and diastolic function (P<0.01 for both) (Fig. 1A). Over a median follow-up of 10.6 years (1,178 patients-years), 24 patients died from a cardiovascular cause and 60 patients had an AVR. Plasma cTnI concentrations predicted AVR and cardiovascular deaths (HR 1.62; 95%CI 1.11-2.36) independent of age, sex, ejection fraction and aortic stenosis severity (Fig. 1B).
Conclusions: In patients with aortic stenosis, cTnI identifies an advanced hypertrophic response and replacement myocardial fibrosis, and predicts AVR and cardiovascular deaths.

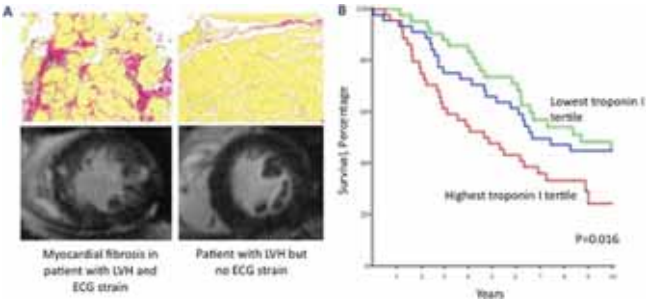

Figure 1. Troponin mechanism and outcomes.

IMPROVING OUTCOMES IN STEMI PATIENTS

P5858 | BENCH
Door to balloon time less than 30 minutes telemetry of 12 canal ecg in the prehospital phase of acute STEMI results for the period of 7 years from 2007 until 2013 including 1050 patients

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Purpose: For the acute ST-elevated myocardial infarction (STEMI) and the primary PCI with announcement there is a "door to balloon time" (DBT) less than 30 minutes demanded. In both Bavarian counties Traunstein and Berchtesgadener Land a "myocardial infarction network" for about 300.000 people with standardised preclinical and clinical procedures for the heart attack was established 2007. The preclinical derived 12-canal ECG is sent automatically to the receiving terminal of the cardiological intensive care unit, is taken up there immediately by an experienced doctor and telephone contact to the emergency doctor is compounded. The aim of this study was to be examined it whether a clear reduction of the DBT can be reached by the systematic preclinical use of the 12 canal ECG telemetry in our administrative districts. The period of the evaluation of the data applies was 7 years from January 2007 to December 2013.
Methods: All involved emergency doctors (n>70) were trained 2 x yearly about sense, purpose and use of the 12 canal ECG telemetry. The acceptance of using the telemetry was determined about the % of ECG with STEMI, which were send by telemetry in the years 2007 and 2013. The DBT time was automatically recorded from the time the patient arrived in the hospital until the time of the balloon-insufflation. Over the period of 7 years from January 2007 to December 2013 1050 patients with the diagnosis "STEMI" were enclosed in the study. Hereof were "STEMI with telemetry by the emergency doctor" (N=389 patients, 37%), without telemetry there are following groups: "STEMI sending from a peripheral hospital" (N=367 patients, 35%), "STEMI from patients come into the emergency room" (N=189 patients, 18%), "TEMI without telemetry by the emergency doctor" (N=105 patients, 10%).
Results: Because of intensive instruction of the emergency doctors the number of telemetry ECG in comparison from the years 2007 to 2013 could be increased from 40% up to 80%. The DBT for the "STEMI with telemetry by the emergency doctor" was in median 28 minutes (SD 14 minutes), for the group "STEMI without telemetry" the DBT was at least 72 minutes (SD 32 minutes). The data distinguished significant.
Conclusion: The telemetry of 12 canal ECG helps the emergency doctor with the diagnosis STEMI and is a very important tool for an optimal preclinical and clinical management for the acute coronary syndrom, above all it helps to prepare the catheter lab in time. With the use of 12 canal ECG telemetry it was possible to get a door to balloon time under 30 minutes (in median 28 minutes) over the period of 7 years.

P5859 | BEDSIDE
The importance of beta-2-agonists in myocardial infarction: findings from the eastern danish heart registry

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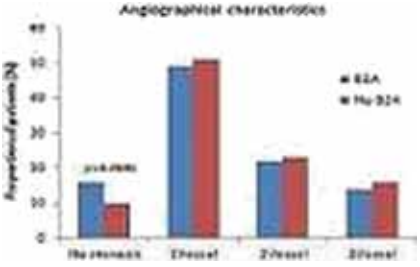
Purpose: β2-agonists are some of the most prescribed drugs worldwide and some studies have suggested that use of B2As is associated with an increased risk of myocardial infarction. Yet, angiographical coronary data and longitudinal outcomes data are sparsed.
Methods: Using a novel data-linkage of the Eastern Danish Heart Registry and nationwide administrative registries (Dec., 1998 to Dec., 2012); we identified a cohort of patients referred for acute coronary angiography due to ST-elevation MI (STEMI). B2A use was determined via prescription claims 12 months prior to date of admission. Clinical and angiographical findings compared between B2A users and non-users. Subsequent mortality associated with the use of B2A was estimated by Cox proportional hazard analyses.
Results: Of 91,124 patients undergoing coronary angiography, 10,521 were acutely referred due to STEMI. Of these, 948 (9%) patients used B2As and were

characterized by older age (median age 68 years vs. 63 years; P<0.0001) and fewer were men (males: 57% vs. 74%; P<0.0001). The number of patients with peripheral vascular disease and hypertension was significant higher among B2A users but comorbidities were otherwise equally distributed in the two groups and so was the frequency of current smokers. For angiographical characteristics; B2A users more often had no acute coronary occlusion (16% in B2A users vs. 10% in non-users; P<0.0001). All-cause mortality during up to 14 years of follow up was significant higher among the B2A -user group compared to the non-user group (Hazard ratio 1.47, 95% CI 1.28-1.69; P<0.0001).



Angiographical characteristics.

Conclusion: Use of B2As is associated with an increased frequency of STEMI without an acute coronary occlusion compared with non-users. Yet, B2A use is also associated with greater long-term mortality.

P5860 | BEDSIDE

Does the right ventricular infarction actually increase the rate of mortality for STEMI patients in PCI era?

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Summary: The aim of the present retrospective observational study was to assess the efficacy of percutaneous coronary intervention (PCI) in patients with ST elevated myocardial infarction (STEMI) with evidence of right ventricular involvement (RVI). The main outcome for patients was in-hospital mortality, and secondary outcomes were heart failure, second-degree and complete AV block, and severe mitral regurgitation.
Methods: In total, we enrolled 535 patients with STEMI. RV involvement was identified from ECG and/or echocardiographic evidence of right ventricular free wall motion abnormalities. RV involvement was diagnosed in 179 (33.5%) patients; 97 patients in the RVI group and 154 patients in the non-RVI group underwent PCI. Groups without PCI consisted of patients who refused the invasive procedure. Patients who had undergone fibrinolytic therapy were excluded from the study.
Results: There was no significant difference in in-hospital mortality between patients with and those without RVI (RVI 16.5% vs. non-RVI 12.6%; p=0.1), but we found that patients with RVI without reperfusion had a higher mortality rate than patients without RVI (RVI 35.4% vs. non-RVI 21.6%; p=0.02). In the RVI group, the rates of heart failure (RVI 29.05% vs. non-RVI 15.4%; p=0.0002), AV blocks II-III d. (RVI 17.9% vs. non-RVI 4.8%; p<0.0001), and severe mitral regurgitation (RVI 21% vs. non-RVI 10.9%; p=0.001) were considerably higher than in the non-RVI group.
PCI in the RVI group was associated with a higher reduction of in-hospital mortality rate (RVI without PCI 35.4% vs. RVI with PCI 8.2%; p=0.00001) than in the non-RVI group (non-RVI without PCI 21.6% vs. non-RVI with PCI 6.3%; p=0.0001). There was no relevant difference in mortality rates between PCI patients with and without RVI (RVI 8.2% vs. non-RVI 6.3%; p=0.6).
PCI reduced the rates of severe mitral regurgitation (12.4% with vs. 31.7% without PCI; p=0.02) and heart failure (19.6% with PCI vs. 40.2% without PCI; p=0.00001) in patients with RVI.
Conclusion: A right ventricle involvement is associated with increased in-hospital mortality and a higher rate of in-hospital complications in STEMI patients. The strategy of PCI results in significant reductions in heart failure, severe mitral regurgitation, and in-hospital mortality in STEMI patients with RV involvement. We have produced the first demonstration that PCI improves the prognosis of STEMI patients with RVI and makes it comparable with that of patients without RVI.

P5861 | BENCH

Aspiration thrombectomy in ST segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: Meta-analysis of 16 randomized trials

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Objectives: Primary percutaneous coronary intervention (PCI) has become the first line of therapy for acute ST elevation myocardial infarction (STEMI) due to providing effective epicardial and myocardial perfusion. However, mortality rate still high in some patients who underwent PCI because of ineffective epicardial and myocardial perfusion. The use of aspiration thrombectomy might be useful in this group but there is contradictory evidence in current trials. Therefore, we performed a meta-analysis that compared aspiration thrombectomy with primary PCI and PCI alone.
Methods: Sixteen trials comparing primary PCI (n=5262) and primary PCI plus aspiration thrombectomy (n=5256) were included in the meta-analysis. We calculated the risk ratio for epicardial and myocardial perfusion, and clinical outcome (all cause death, re- Infarction, target vessel/lesion revascularization, stent thrombosis and cerebrovascular accident) and composite major adverse cardiac outcome (all cause death, re- Infarction, target vessel/lesion of revascularization).
Results: In aspiration thrombectomy group post- procedural TIMI III flow, post-procedural MBG II- III flow and post-procedural ST resolution on ECG were more frequent than PCI alone group. The results revealed that all cause death incidence was comparable between thrombectomy arm (2.9%) and conventional primary PCI arm (3.4%) (HR: 0.861, 95% CI: 0697-1062, p=0.163). Besides, re-infarction frequency was 0.8% in the thrombectomy arm and 1.3% in the conventional primary PCI arm (HR: 0.632, 95% CI: 0433 to 0923, p=0.017). While TVR/TLR frequency was 3.9% in thrombectomy arm, it was 5.2% in the conventional primary PCI arm (HR: 0.795, 95% CI: 0664-0952, p=0.013). MACE frequency was 7.3 in thrombectomy arm and it was 9.1% in the conventional primary PCI arm (HR: 0.797, 95% CI: 0704-0903, p<0.001).
Conclusion: Aspiration thrombectomy improved epicardial and myocardial perfusion, reduced the rate of re- Infarction and target vessel / lesion of revascularization, however did not reduce the rate of mortality.

P5862 | BEDSIDE

Outcomes in patients with cardiogenic shock following percutaneous coronary intervention in the contemporary era: an analysis from the british cardiovascular intervention society (BCIS) database

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Background: Cardiogenic shock (CGS) remains the dominant cause of death among patients hospitalised with acute myocardial infarction (AMI). Mortality rates associated with CGS were reported to be as high as 80% in the 1970s, but falling to 50-60% in the 1990s. It is unclear whether recent advances in pharmacological and interventional strategies have resulted in further improvements in short- and long-term mortality and furthermore which factors are associated with current adverse outcomes.
Purpose: To determine mortality rates (at 30-day, 90-day, and 1-year) among CGS patients in the UK undergoing percutaneous coronary intervention (PCI) for AMI in the contemporary treatment era and to determine predictors of mortality.
Methods: A retrospective analysis of prospectively collected data for patients undergoing PCI in the setting of CGS submitted by all PCI centres within the United Kingdom from January 2005 to July 2012, as recorded in the British Cardiovascular Intervention Society (BCIS) PCI database.
Results: The initial dataset consisting of 501 117 PCI procedures from all centres in the UK was used as the basis for the analysis. Of these, 6 357 patients underwent PCI for AMI and in the setting of CGS in England and Wales and form the analysed cohort. The mortality rate at 30-day, 90-day and 1-year was 37.3%, 39.9% and 44.2% respectively. On multiple logistic regression analysis the following factors were associated with increased mortality at 1-year: age (Odds Ratio [OR] for each year increment of age: 1.05; 95% Confidence Interval [CI]: 1.05-1.06, p<0.0001), diabetes mellitus (OR: 1.35; 95% CI: 1.11-1.63, p=0.0026), history of renal disease (OR: 2.20; 95% CI: 1.64-2.94), use of artificial mechanical ventilation (OR: 2.69 95% CI: 2.23-3.24, p<0.0001), intra-aortic balloon pump (IABP) use (OR: 1.90; 95% CI: 1.62-2.22, p<0.0001), and need for left main stem PCI (OR: 1.66; 95% CI: 1.33-2.07, p<0.0001).
Interpretation: In this large UK cohort of patients undergoing PCI in the context of CGS, mortality remains high in spite of the use of contemporary PCI strategies. Further improvements in the early detection and management of CGS are still required. This remains an area that requires focussed research investment.

P5863 | BEDSIDE

Efficacy of radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes

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Purpose: A recent trial showed that radial access for PCI in STEMI patients (pts) improved 30-day clinical outcome compared with femoral access. Aim of this study was to assess the efficacy of radial access versus femoral access in pts with acute coronary syndromes (ACS) who underwent coronary angiography with possible intervention.
Methods: This is a single-centre, large, prospective observational registration of

all STEMI and NSTEMI pts who underwent coronary angiography and/or (primary) PCI in the period January 2010 – December 2012. Primary endpoint was 30-day all-cause mortality. Choice of access was left to the discretion of the cardiologist. All safety- and clinical parameters, were performed by 2 independent investigators.
Results: Of the 3384 ACS pts, coronary angiography was performed in 2950/3384 (89%) and in 671/2950 (23%) pts by radial access. PCI was performed in 2181/2950 (74%) of the pts. No differences in baseline or angiographic characteristics were present between radial vs femoral access patients except for diagnosis of STEMI: 54.6% vs 60.0%, p=0.011, IABP use: 1.1% vs 6.7%, p<0.001, and Killip class≥2: 8.6% vs 12.9%, p=0.012. The primary endpoint occurred less often in the radial group as compared to the femoral group (1.7% vs 4.8%, p<0.014). Also 30-day net adverse clinical events (NACE) occurred less often in the radial group (6.3% vs 10.8%, p=0.001). After multivariate correction, radial access remained an independent predictor for 30-day mortality (HR 0.433; 95% CI, 0.221 – 0.850, p=0.015, see Fig. 1).

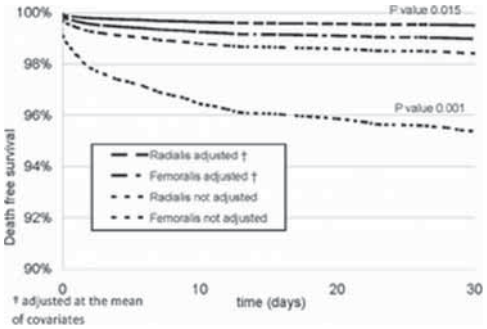

Figure 1. 30-day mortality Kaplan Meier curve.

Conclusion: Radial access in all comer ACS patients significantly reduced 30-day mortality and 30-day NACE compared with femoral access, with similar PCI success. Radial access remained an independent predictor for 30-day all-cause mortality.

P5864 | BEDSIDE
Surgical outcomes of patients with acute coronary syndromes undergoing coronary artery bypass grafting: Results from the North-Rhine-Westphalia surgical myocardial infarction registry

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Objectives: To evaluate in-hospital mortality of patients referred to urgent coronary artery bypass grafting (CABG) with acute coronary syndromes (ACS), including ST-elevation or non ST-elevation myocardial infarction (STEMI/NSTEMI) or unstable angina (UA).
Methods: Between 01/2010 and 05/2012 patients undergoing urgent CABG with ACS were prospectively entered into a registry by four participating cardiac surgery centres in North-Rhine-Westphalia. Demographic data and over one-hundred perioperative variables were recorded, including in-hospital all-cause mortality. After univariate analysis, relevant perioperative variables were entered into a multivariate logistic regression model to identify independent predictors for in-hospital mortality.
Results: A total of 1197 patients (age 68±11 yrs, males 78%, log. EuroSCORE 24±21%) were admitted to CABG surgery with STEMI (25%), NSTEMI (50%) or UA (25%). Three-vessel coronary artery disease was present in 80% with mainstem involvement in 46% of patients. On-pump CABG surgery was performed in 92% (CPB-time, 103±43 min, aortic cross-clamp time, 60±26 min; 53% blood cardioplegia) with a mean of 2.5±0.7 bypass grafts and 91% LITA use. Overall in-hospital mortality was 7.4%, with 12.7% in STEMI patients, 5.6% in NSTEMI and 5.0% in patients with UA (P<0.001). Multivariate logistic regression analysis revealed age, female gender, preoperative troponin I, LVEF, on-pump surgery and the need for ECMO therapy to be independently predictive for in-hospital mortality (P<0.05). Importantly, the preoperative use of aspirin/clopidogrel, ß-blockers, or statins, the use of preoperative IABP support as well as the type of cardioplegia (crystalloid/blood) were not associated with in-hospital mortality.
Conclusions: CABG in patients with ACS is still linked to substantial in-hospital mortality. Especially for patients with STEMI reliable identification of preoperative predictors is mandatory to improve surgery outcomes.

TAVI: WHAT PREDICTS OUTCOME?

P5865 | BEDSIDE
Impact of mixed aortic valve stenosis on outcomes and postprocedural paravalvular aortic regurgitation in patients undergoing TAVI: results from the international multicentric registry PRAGMATIC

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Background: Residual postprocedural paravalvular aortic regurgitation (PPAR) is one of the main complications of transcatheter aortic valve implantation (TAVI) procedure. Only few data are available on the impact of baseline aortic regurgitation (AR), in patients affected by severe aortic stenosis undergoing TAVI, on clinical outcomes and PPAR.
Objectives: The aim of this study was to assess the impact of baseline AR on incidence of PPAR and clinical outcomes.
Methods: Data from databases of 4 experienced European centers were pooled together and analysed. AR grade was defined according to the European Association of Echocardiography (EAE) guidelines. Population was subdivided in patients affected by Pure Aortic Stenosis (PAS, <1+/3+) and by Mixed Aortic Stenosis (MAS, ≥1+/3+). Study objectives were the incidence of PPAR, Valve Academic Research Consortium 2 (VARC-2) outcomes at 30 days, 1 year and 2 years, and long-term follow-up total and cardiovascular mortality.
Results: In total, 1091 patients were included: 432 (39.5%) with MAS and 659 (60.4%) with PAS. At 30 days, there were no differences in all-cause (6.4% vs. 6.3%; p=0.930) and cardiovascular mortality (5.5% vs. 4.2%; p=0.315), however a greater incidence of major bleeding (23% vs. 16.5%; p=0.011), spontaneous myocardial infarction (2% vs. 0.3%; p=0.019) and PPAR ≥1+/3+ (43% vs. 27%; p<0.001) was observed in patients with MAS. Conversely, no differences were found in the incidence of PPAR ≥2+/3+ (3% vs. 2%; p=0.137). Of note, MAS resulted an independent predictor of PPAR ≥1+/3+ at multivariable analysis. At a median follow-up period of 421 days (IQR 252 – 710), patients with MAS had a greater all-cause (30% vs. 24%; p=0.047) and cardiovascular mortality (17% vs. 12%; p=0.023).
Between MAS and PAS patients that developed PPAR ≥1+/3+, no difference in mortality at 30 days and at long-term follow-up was present. Conversely, in patients that developed PPAR ≥2+/3+ the presence of baseline MAS was associated with a trend to lower long-term all-cause and cardiovascular mortality (46% vs. 73%, p=0.188 and 17% vs. 50%, p=0.095).
Conclusions: In the present cohort, baseline MAS has a high prevalence and is associated with a higher incidence of PPAR and increased all-cause and cardiovascular mortality when compared to patients with baseline PAS at a median follow-up period of 421 days. In patients who developed PPAR ≥2+/3+, baseline MAS trended to be associated with improved long-term survival.

P5866 | BEDSIDE
Risk factors and clinical significance of intra-procedural haemodynamic instability in patients undergoing transcatheter aortic valve implantation

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Objectives: The aim of this study was to investigate the causes, risk factors and clinical significance of haemodynamic instability (HI) during TAVI procedure.
Methods: From November 2007 to September 2013 all patients consecutively treated in our center were retrospectively analyzed. HI was defined as a drop of mean arterial pressure ≥20 mmHg with a heart rate (HR) ≥100 or ≤50 beats/min for ≥1 min. Causes of HI were broadly classified in those occuring post-preparatory balloon aortic valvuloplasty (PBAV), in patients in whom a PBAV was performed, and post-valve implantation (VI). Each group was compared with a control group where intraprocedural HI did not occur.
Results: Overall, of 538 patients that underwent TAVI, 35 (7.4%) developed HI. Of these 18/453 (3.9%) developed HI after PBAV, while 19/538 (3.5%) developed HI after VI. Causes of HI after PBAV included severe aortic regurgitation (AR; 50%), new-onset arrhythmia (44.4%) and aortic annulus rupture (5.5%). Causes of HI after VI included aortic dissection (10.5%), cardiac tamponade (73.6%), coronary obstruction (10.5%) and severe AR (5.2%). Patients that developed HI after PBAV had higher all-cause and cardiovascular mortality at 30 days (respectively, 11.1% vs. 3%, p=0.023; and 11.1% vs. 1.8%, p=0.009), more frequently required urgent cardiothoracic surgery (11.1% vs. 1.4%; p=0.002), a 2° valve (12.5% vs. 3%; p=0.038), had higher incidence of arrhythmias (43.8% vs. 19.2%; p=0.016) and cardiac tamponade (12.5% vs. 2.7%; p=0.027). No differences were found in mortality at 2 years of follow-up. Predictors of post-PBAV HI were BAV diameter, LVEDP and moderate-severe pulmonary hypertension.
Patients that developed HI after VI had higher rates of all-cause and cardiovascular mortality at 30 days (respectively, 26.3% vs. 2.7%, p<0.001; and 21.1%

vs. 1.9%, p<0.001), acute kidney injury (57.9% vs. 25.3%; p=0.002), urgent cardiothoracic surgery (31.6% vs. 0.8%; p<0.001), valve embolization (15.8% vs. 2.6%; p=0.001) and need for a 2° valve (21.1% vs. 3.7%; p<0.001). Finally, a higher all-cause and cardiovascular mortality was observed at 2-year follow-up (36.8% vs. 16.9%, p=0.025; and 26.3% vs. 9.3%; p=0.015). Predictors of HI after VI were cover index >10, valve implantation without PBAV and mean aortic valve gradient.
Conclusions: The main causes of HI after PBAV were severe AR and new-onset arrhythmia, while after implantation was cardiac tamponade. HI after PBAV had a higher 30-day mortality but did not affected long-term survival. Conversely, HI after VI had a negative impact on both 30-day and long-term survival.

P5867 | BEDSIDE
Cost-utility of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis: Prospective observational study

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Purpose: Studies assessing cost-effectiveness of transfemoral Edwards Sapiens (ES) TAVI vs aortic valve replacement (AVR) are scanty, use data from a single randomized clinical trial and differ depending on the health system (US vs Europe). In addition there are no data concerning Medtronic Corevalve (MC). We sought to estimate the cost-utility of the two transfemoral TAVI modalities vs conventional surgery using data from "real life" patients.
Methods: Patients were recruited prospectively in 7 hospitals. Follow-up was performed at 1, 3 and 6 months after intervention. We measured utility from EQ5D data. We calculated differences in costs and QALYs between ES or MC versus AVR and the incremental cost-utility ratio (ICER) comparing ES vs AVR and MC vs AVR. Additionally, we performed net-benefit regressions on different willingness to pay threshold values (ranging from 0 to €50,000) and we estimated the adjusted ICERs. A willingness to pay threshold of 30,000 €/QALY was assumed for interpreting the results. Additional analyses were performed for different subgroups and scenarios.
Results: Data from 186 patients were analyzed: 48 in the ES-TAVI group, 86 in the MC-TAVI group and 52 in the AVR group. Mean logistic Euroscore (SD) was: ES: 14.3 (10.4), MC: 14.7 (9.9), AVR: 14.5 (6.9). Overall cost of ES-TAVI was €7,202 higher than AVR and the QALY benefit was 0.045, resulting in an ICER of 161,086 €/QALY. The adjusted ICER using the net-benefit approach was 131.000€/QALY. The cost of MC-TAVI was €7,476 higher than AVR and the QALY benefit was 0.003, resulting in an ICER of 2,451,568 €/QALY. The adjusted ICER was not estimable because MC-TAVI was non beneficial when adjusting for baseline characteristics. The results did not substantially change considering additional analyses except for: 1) In patients with preoperative higher serum creatinine levels ES-TAVI was dominant and the adjusted ICER was 6,266 €/QALY for MC-TAVI; 2) a 30% reduction in the cost of the TAVI device lead to ES-TAVI being dominant over AVR; and 3) an increase of 30% in all costs except the price of the device lead to an adjusted ICER of 33,186 €/QALY for ES-TAVI.
Conclusions: In our's country setting, transfemoral TAVI is not likely to be cost-effective compared to AVR. TAVI appears to be cost-effective in specific subgroups of patients. In a European setting, the high cost of the valve in relation to global health care costs is the main determinant of the unfavorable cost-utility of ES-TAVI. A reduction of the valve device price would increase the probability of TAVI being cost-effective and spread its use.

P5868 | BEDSIDE
Cognitive trajectory after transcatheter aortic valve implantation - long-term results

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Background: Transcatheter aortic valve implantation (TAVI) is known to be associated with silent cerebral injury, which could contribute to cognitive impairment. Considering its increasing use, thorough longitudinal investigation of cognitive trajectory after TAVI is pivotal.
Methods and results: Repeatable battery for the assessment of neuropsychological status was performed before (E1), 3 days (E2), 3 months (E3), 1 (E4) year, and 2 years (E5) after TAVI. Baseline characteristics, procedural data, imaging parameters of brain injury (diffusion-weighted MRI), and the use of conceivable neuroprotective approaches were investigated for their effect on cognitive function. Cognitive performance was investigated in 111 patients (mean log EuroSCORE, 30±13%). Global cognitive function (repeatable battery for the assessment of neuropsychological status total score) increased transiently at E2 (P=0.02) and was comparable with baseline levels at E3, E4, and E5. Six patients (5.4%) demonstrated early cognitive decline. Persistence and late onset were seen infrequently (n=3, 2.7% and n=4, 3.6%, respectively). Hence, early cognitive decline was ruled out in 105 patients (94.6%), and a majority of patients (91%) demonstrated sustained cognitive performance throughout all investigated time points. Interestingly, only patient age (P=0.012), but not prior cerebrovascular events, cognitive status, direct TAVI, cerebral embolism in diffusion-weighted MRI, or the use of a cerebral embolic protection device was found to be independently associated with cognitive decline, linking higher age to cognitive impairment along the first 2 years after TAVI.
Conclusions: Long-term cognitive performance was preserved in the great majority (91%) of patients throughout the first 2 years after TAVI, despite the high intrinsic risk for cognitive deterioration.

P5869 | BEDSIDE
In-hospital events in a propensity matched cohort of percutaneous vs surgical aortic valve replacement patients

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Background: Transaortic valve implantation (TAVI) is an option in patients (p) with severe aortic stenosis deemed inoperable or of high surgical risk. However, direct comparisons between surgical aortic valve replacement (SAVR) and TAVI are subject to several limitations, among them selection bias
Aim: Evaluate baseline characteristics and in-hospital outcomes of p submitted to TAVI versus SAVR after propensity matching in a real world cohort.
Methods: 941 consecutive p submitted to AVR (TAVI n=49;biological SAVR n=892) were analysed. Multivariate logistic regression was used to determine baseline predictors of treatment by TAVI. These variables were used to create a propensity-score model.P were then submitted to nearest neighbour matching in a 1:4 ratio (1 TAVI p for 4 SAVR p).
Results: In pre-matching analysis, significant differences were found on baseline characteristics regarding age (TAVI vs SAVR, 80,10±6,85 vs 73,52±8,04), Log Euroscore (15,83±9,31 vs 8,09±6,66), left ventricular (LV) dysfunction (53,06% vs 19,84%),chronic kidney disease (38,78% vs 19,17%) and chronic obstructive pulmonary disease (COPD: 26,53% vs 9,53%) - p<0,001 for all. In the SAVR group post propensity matching, there were no significant differences vs TAVI p (age: 78,08, Log Euroscore: 17,06, LV dysfunction: 58,67%, CKD 53,06%, COPD: 27,55%,p=NS for all).The results for in-hospital events are presented in Table 1.

Table 1

Group	TAVI	SAVR post matching	p
n	49	188	
Mortality	8,16%	9,18%	NS
Length of ICU stay	6,68	6,05	NS
Stroke	0,00%	3,33%	NS
Acute kidney injury	12,24%	35,20%	0.0037
Permanent pacemaker	26,53%	1,53%	<0.001
Bleeding with reintervention	4,08%	2,04%	NS
Infection	4,08%	2,04%	NS

Conclusions: In this propensity-matched cohort of p submitted to TAVI and SAVR, in-hospital mortality was similar. Different complications were observed in the two groups, with pacemaker implantation more likely in the TAVI group and acute renal injury in the SAVR group. Both modalities were similar in respect to other in-hospital events

P5870 | BEDSIDE
One year of outpatient percutaneous coronary intervention: safe, comfortable and money saving

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Purpose: To start an outpatient percutaneous coronary intervention (PCI) program and to analyse its safety, patient satisfaction and the potential cost reduction.
Methods: Patients submitted for coronary angiography and elective PCI were evaluated during 2013. Those older than 80 years, with left ventricular ejection fraction ≤35%, with renal glomerular filtration rate ≤30 ml/min and allergic to antiplatelet drugs were excluded. In case of non-high risk coronary anatomy and no PCI complications, they were selected for same-day discharge after 6 hours of clinical surveillance, checked the morning after and followed for 1 month. Then, we conducted a patient satisfaction survey.
Results: 72 patients were admitted as candidates for day-case PCI. 47 (65%) stayed overnight at hospital. Reasons for non-discharge included high-risk coronary anatomy or PCI complications (n=44, 94%),use of abciximab (n=1, 2%) and chest pain during observation (n=2, 4%). 25 patients (35%) went home after a mean time at hospital of 8 hours 45 min ± 1 hour 12 min.
Safety: Minor radial haematoma occurred in 3 patients and slight changes in repolarization on electrocardiography were showed in other 3 patiens, but this did not preclude hospital discharge. None patient needed to call medical emergency

services during the night at home. The morning after, there were no complications at the puncture site, 2 patients showed negative T waves on electrocardiography and an asymptomatic new onset atrial fibrillation was diagnosed and solved with cardioversion. 4 patients had Troponin I levels above 1 ng/ml. At one month follow up there were 2 (8%) adverse events: 1 subacute bare-metal stent thrombosis at 7th day treated with primary PCI, 1 lower digestive hemorrhage leading to diagnose of colon carcinoma. Both would not be avoided in case of in-hospital overnight observation.
Patients' opinion: High patient satisfaction score (ranges from 1 to 5, mean 4,4±0,9) in the survey indicated that day-case PCI was popular with the patients. 22 patients (88%) would choose same-day discharge in case they should repeat PCI.
Expense: In our hospital, the mean cost of PCI is 2.480 €. A day of hospitalization costs 400 €. Performing PCI as a day-case procedure minimizes the problems of bed availability and reduces overall expense by 16 percent.
Conclusions: In selected patients, elective day-case PCI appears feasible and safe, well valued by patients and cost saving.

P5871 | BEDSIDE
Impact of very severe left ventricular dysfunction on outcomes after transcatheter aortic valve implantation

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Background: Transcatheter aortic valve implantation (TAVI) seems to have better outcomes on high-risk patients as compared to conventional surgery in patients with severe left ventricular dysfunction (LVEF≤35%). However, the range of dysfunction included in the term "severe" is wide and up to 10% of TAVI patients present deeper LV dysfunction (≤25%). There is a lack of data concerning this subgroup.
Objective: To determine prognosis of patients with severe LV dysfunction and to compare the outcomes with the subgroup presenting deeper dysfunction.
Methods: We enrolled 76 consecutive patients with severe aortic stenosis who underwent TAVI with severe LV dysfuntion; 52 (68.4%) presented LVEF=35-25% and 24 patients (31.6%) LVEF≤25%.
Results: Mean age was 79±8 yrs and 84.2% were in NYHA class III-IV/IV. Mean LVEF was 29±6% and mean gradient 33±14 mmHg at baseline, 32±11% and 9±4 mmHg at 1-month follow-up, respectively. Mean LogEuroSCORE was 29.0±15.2. At 1-year follow-up readmission rate was 35.5% and cumulative mortality 32.9%.
Patients with deeper LV dysfunction (≤25%) were more frequently males 87.5% vs. 73.5%, p=0.032 and with higher LogEuroSCORE 34.9±14.5% vs. 27.0±15.0%, p=0.036, but no differences in STS-score 9.7±5.2% vs. 8.8±5.2%, p=0.492. They also presented lower mean aortic gradients (27±11 vs. 36±15%, p=0.024) and mean LVEF was 21±4 vs. 33±2%, p<0.001. No differences in baseline NYHA class, NTproBNP values, or mitral regurgitation at baseline were found, however, the rate of left bundle branch block (LBBB) was as high as 41.7% vs. 11.5%, p=0.003, and previous pacemaker/defibrillator in 33.3 vs. 19.2%, p=0.179.
No procedural differences were found. Postprocedurally, LVEF differences persisted at 1-month follow-up (28±10 vs. 35±11%, p=0.016) but only those with lower LVEF experienced a significant improvement (mean increase of 7±6%), p<0.001.
The incidence on new-onset LBBB was higher in patients with lower LVEF (45.8 vs. 23.1%, p=0.045), but not the rate of new permanent pacemaker.
No signficant differences in terms of cumulative mortality at 1-year existed (33.3 vs. 32.7%, p=0.956) but the rate of re-hospitalizations was almost twice (50.0% vs 28.8%, p=0.073).
Conclusions: Patients with lower LVEF (≤25%) presented higher risk profile, however their mortality rate was not higher at 1-year (as predicted by STS-score but not by LogEuroSCORE). These patients presented higher rate of conduction disturbances. Improvement of LVEF occurred mainly in those patients with lower LVEF, in spite of that, they presented more re-hospitalizations in the follow-up.

EPIDEMIOLOGY- NEW INSIGHTS

P5872 | BEDSIDE
Reduced aortic size without changes in arterial stiffness in young adults born preterm

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Preterm birth is associated with reduced cardiac size, likely due to premature shift from low resistance in-utero circulation to high resistance systemic circulation. We used cardiac magnetic resonance (CMR) and non-invasive measures of arterial stiffness to determine whether there are proportional reductions in aortic size in preterm born individuals which might lead to a change in arterial stiffness important to blood pressure.
204 individuals aged 20-30 years underwent detailed cardiovascular phenotyping. 102 had been followed prospectively since preterm birth and 102 were born at term to uncomplicated pregnancies. CMR imaging (Siemens 1.5T scanner) was performed to measure cardiac volumes and aortic structure at multiple levels of the thoracic and abdominal aorta. Blood pressure was assessed peripherally and centrally. Arterial function was assessed by Sphygmacor tonometry (to measure carotid-femoral pulse wave velocity (PWV)) and cardio-ankle vascular index (CAVI), a blood pressure adjusted measure of arterial stiffness.
The preterm cohort had a mean gestational age of 30.3 weeks (±2.5), birth weight 1297g (±286) and current age of 25.1 years (±1.4), compared to the term cohort of 39.6 weeks (±0.9), 3460g (±417) and 25.0 years (±2.6). Resting mean arterial blood pressure was elevated in the preterm cohort 89.1 mmHg (±7.4) compared to 83.5 mmHg (±7.1) in the term cohort (P<0.001). In the preterm cohort, the aorta lumen cross-sectional area was significantly smaller in the thoracic descending (1.21 cm^2/m^2 (±0.18) and 1.46 cm^2/m^2 (±0.24), P<0.0001) and abdominal aorta (0.70 cm^2/m^2 (±0.19) and 1.05 cm^2/m^2 (±0.19), P<0.0001) compared to the term cohort. The aorta luminal areas correlated with left ventricular end diastolic volumes in both preterm (r^2=14%, P=0.0003) and term cohorts (r^2=26% P<0.0001). However the blood pressure differences between groups were not associated with the degree of reduction in aortic size in the preterm (r^2<1% P=0.43) or term cohort (r^2=2% P=0.22). In the preterm cohort PWV was significantly increased when measured from aorta to tibial artery (6.4 m/sec (±0.6) and 6.1 m/sec (±0.4), P=0.009) and carotid to femoral artery (5.8 m/sec (±0.8) and 5.5 m/sec (±0.6), P<0.001). However, CAVI and PWV adjusted for mean arterial pressure were not significantly different between groups.
Reductions both in aortic and cardiac size are proportional in individuals born preterm. However the changes do not appear to explain the differences in blood pressure. When blood pressure is accounted for arterial stiffness is unchanged in preterm born individuals.

P5873 | BEDSIDE
Aortic root diameter and risk of cardiovascular events in a general population: the PAMELA study

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Aim: Data on the association of aortic root diameter (ARD), as assessed by echocardiography, with incident cardiovascular morbidity and mortality in the general population are scanty and limited to elderly individuals. Thus, we investigated the value of ARD in predicting cardiovascular events in the PAMELA population.
Methods: At entry 1860 subjects (mean age 50+14, 50.6% men) underwent diagnostic tests including laboratory investigations, office and out-of office blood pressure measurements (home and 24-hour ambulatory BP monitoring), and echocardiography. ARD was measured at the level of Valsalva's sinuses and indexed to body surface area (BSA) and height.
Results: Over a follow-up of 148 months, 139 non-fatal or fatal cardiovascular events were documented. After adjustment for age, sex, BP, fasting blood glucose, total cholesterol, and use of antihypertensive drugs, ARD indexed to BSA (HR for 1 unit increase = 2.48, 95%CI 1.13-5.44, p=0.02), and ARD indexed to height (HR=2.69, 95%CI 1.21-5.97, p=0.01) but not absolute ARD (HR=1.38, 95%CI 0.85-2.24, p=0.19) predicted an increased risk of cardiovascular events
Conclusions: Our results for the first time show that ARD indexed to body size is predictive of incident non-fatal and fatal cardiovascular events among middle-aged subjects in the community and support the view that assessment of ARD might contribute to refine cardiovascular risk stratification and preventive strategies in the general population.

P5874 | BEDSIDE
Longitudinal association of carotid atherosclerosis with depressive symptomatology in late life: the 3C study

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Purpose: Vascular disease has been hypothesized to increase the risk of depression in late life, but evidence form prospective studies is currently lacking. We investigated the longitudinal association of carotid atherosclerosis with depressive symptomatology in older adults.
Methods: A cohort of community-dwelling individuals 65 to 85 years of age was examined for carotid plaque presence (CPP) and common carotid artery intima media thickness (CCA-IMT) at baseline and followed up after 2, 4, 7 and 10 years. At baseline and follow-up examinations, depressive symptomatology was measured using the Centre for Epidemiologic Studies Depression Scale (CES-D). Depressive symptoms (DS) were defined using validated cut-offs (CES-D score >16 in men and >22 in women). We evaluated associations of CPP and CCA-IMT at baseline with CES-D score at follow-up examinations using linear mixed mod-

els. For a more clinical perspective, the likelihood of DS at follow-up associated with CPP and CCA-IMT at baseline was estimated using generalized estimating equations.
Results: Among 4,125 participants (mean age 73.4 years, 57.8% female) without lifetime major depression and free of DS and dementia at baseline, a total of 1,973 (47.8%) showed CPP, and mean CCA-IMT was 0.71 (standard deviation [SD] 0.12) mm. Baseline CPP was associated with a significantly higher CES-D score at the 10-year follow-up in men (+1.40, standard error [SE] 0.38, $p<0.001$), but not in women, after adjustment for age, study centre and antidepressant use at follow-up examinations. Baseline CPP was also associated with a significantly increased likelihood of DS at follow-up examinations in men (odds ratio 1.36, 95% confidence interval 1.02-1.80), but not in women. One SD increase in baseline CCA-IMT was associated with a significantly higher CES-D score at the 10-year follow-up in men (+0.38, SE 0.19, p=0.046) and women (+0.56, SE 0.20, p=0.005). The association between baseline CCA-IMT and DS at follow-up examinations was non-significant in both sexes. Results were consistent when further adjusting for cardiovascular risk factors and cognitive functioning at baseline and for coronary heart disease and stroke events as well as incident dementia during the 10-year follow-up.
Conclusions: Baseline CPP was associated with a higher CES-D score and an increased likelihood of DS at follow-up in older men, and baseline CCA-IMT was associated with a higher CES-D score at follow-up in older men and women. These associations lend support to the hypothesis that vascular disease increases the risk of depression in late life.

P5875 | BEDSIDE
Ethnic differences in the effect of the Framingham risk factors on atherosclerosis and cardiovascular events in the USE-IMT cohort

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Background: Cardiovascular disease (CVD) is an important cause of morbidity and mortality, not only in Caucasians, but also in other ethnic groups worldwide. Yet, one may wonder whether it is appropriate that most primary prevention programs and risk scores are based on data derived from mostly or even exclusively Caucasian people. Therefore we investigated ethnic differences in the magnitude of the relation of the Framingham risk factors with atherosclerosis (measured by mean common carotid intima-media thickness (CIMT)) and cardiovascular events.
Methods: For our analyses we used the USE-IMT cohort, a large ongoing individual participant data meta-analysis involving 17 population-based cohorts worldwide. From the entire cohort 60,211 participants were selected who were free from CVD at baseline and had known ethnicity (Caucasian, Black, Asian or Hispanic). First, we applied linear regression and Cox regression on a model containing the Framingham risk factors and ethnicity for mean common CIMT and CVD events (first-time myocardial infarction or stroke), respectively. Then we repeated these analyses with the model containing interaction terms for all Framingham risk factors with ethnicity. Finally, we assessed whether the magnitude of the relations (betas from linear regression, hazard ratios from Cox regression derived from the interaction models) for the ethnic groups were significantly different from that found for Caucasians.
Results: When common CIMT was used as an outcome, the magnitude of the relation was significantly different from Caucasians for age (lower in Blacks and Hispanics), systolic blood pressure (higher in Asians), HDL-cholesterol (lower in Blacks) and smoking (lower in Blacks). For CVD events, the magnitude of the relation was significantly different from Caucasians for age (lower in blacks) and total cholesterol (higher in Blacks).
Conclusion: The relations of the Framingham risk factors with atherosclerosis and CVD had similar directions across ethnic groups. Yet, the magnitude of the relations differed among ethnic groups. Our study may shed light on the focus of primary prevention programs among other ethnicities, and demonstrates the need for ethnicity-specific risk scores.

P5876 | BEDSIDE
Gender differences in lifetime risk and first manifestation of cardiovascular disease: a competing risks analysis from the population-based Rotterdam Study

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Purpose: Knowledge on the first manifestation of cardiovascular disease (CVD) is relevant for primary prevention. Data on gender differences of first manifestations of CVD are scarce, and no studies have compared multiple first CVD manifestations between men and women in a competing risks framework.
Methods: We used data from 8419 participants (60.9% women), aged 55 years and older, of the prospective population-based Rotterdam Study cohort to estimate lifetime risks of CVD and its first fatal or nonfatal manifestations (coronary heart disease [CHD], cerebrovascular disease, heart failure, and other CVD death) at various ages. Competing risks among the different first CVD manifestations and non-cardiovascular death were taken into account in all analyses. Regression models were adjusted for cardiovascular risk factors.
Results: During up to 20.1 years of follow-up, 2888 participants developed CVD and another 1532 died from non-cardiovascular causes. At age 55, lifetime risk of CVD was similar with 67.1% (95%CI 64.7-69.5) for men and 66.4% (95%CI 64.2-68.7) for women. Cumulative incidence of CVD in men increased steadily with age, whereas in women up to the age of 70 CVD incidence remained low and increased only thereafter. Women were less likely than men to have CHD as a first manifestation (HR 0.51; 95%CI 0.43-0.60), but more likely to have cerebrovascular disease (HR 1.16; 95%CI 1.00-1.33). Compared to CHD, competing cause-specific hazards for were higher for cerebrovascular disease ($P<0.001$) and heart failure (P=0.010) as the first CVD manifestations in women than in men. CHD accounted for 40.5% of the first CVD manifestations in men, whereas cerebrovascular disease and heart failure together represented 71.2% of the first manifestations in women. When restricting the analyses to hard atherosclerotic CVD outcomes, lifetime risk was 43.2% (95%CI 40.7-45.6) for men and 38.1% (95%CI 36.2-40.1) for women. For hard events, CHD remained the most common first manifestation in men at all ages (44.9% to 54.4%), while in women ischemic stroke was the predominant CVD presentation (59.1% to 63.9%).
Conclusions: Men and women of middle age have similar lifetime risks of CVD. Two out of three face some form of CVD during their lifespan, underlining that primary prevention of CVD is of paramount importance. Gender differences in the first manifestation of CVD are, however, large: CHD accounts for nearly half of the first CVD revelations in men, whereas CVD unveils itself with cerebrovascular disease or heart failure in over 70% of women. This emphasizes the priority of stroke and heart failure prevention in women.

P5877 | BEDSIDE
Association between pneumococcal vaccination and cardiovascular outcomes: a systematic review and meta-analysis of cohort studies

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Purpose: Streptococcus pneumoniae is the most common cause of community-acquired pneumonia (CAP) and CAP-related mortality in adults. It has been suggested that pneumococcal vaccination (PV) could protect patients from cardiovascular events by reducing pneumonia severity or even preventing it. We conducted a meta-analysis of cohort studies for determining the ability of PV to protect from the risk of CV events and to dissect factors influencing this ability.
Methods: A comprehensive search of electronic databases was conducted through January 2014. Cohort studies that reported relative risk (RR) estimates with 95% confidence intervals were included. Two reviewers extracted data independently and summary estimates of association were obtained using a fixed- or random-effects model.
Results: Eleven studies were included (332,267 participants, mean follow-up 20.1 months, 12 full-text articles)/ The pooled relative risks (RRs) for total CV events and CV mortality were 0.86 (95% confidence interval: 0.76 to 0.97), 0.91 (95% CI: 0.86 to 0.98), respectively, for subjects with PV versus subjects without PV (Figure). Protective ability for total CV events was more prominent in high CV risk populations and with older age. The protective role of PV was attenuated after 1 year (RR: 0.72, 95% CI: 0.59 to 0.88 vs. RR: 1.03; 95% CI: 0.93 to 1.14; P=0.002, for follow-up >1 year vs <1 year, respectively). The protective ability of PV increased as the presence of CV and pulmonary disease increased, while whether patients were vaccinated for influenza did not influence the protective role of PV. Regarding MI and cerebrovascular events, the protective role of PV was statistically significant only in the elderly (RR: 0.90; 95% CI: 0.817 to 0.999 and RR: 0.86; 95% CI: 0.75 to 0.99, respectively).
Conclusion: PV is associated with decreased risk of CV events and CV mortality, while the protective value of PV for total CV events increases at older ages and in high CV risk subjects and decreases as the time elapses from the PV. PV decreases the risk of MI and cerebrovascular events in the elderly.

P5878 | BEDSIDE
Patient population size and mortality benefit: key drivers of cardiovascular healthcare cost decisions

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Purpose: Pharmaceutical innovation is costly, especially for drugs and devices required to show a mortality benefit. Value assessments for reimbursement decisions are challenging in this regard. The aim of this study was to explore correlations between mortality benefit, patient population size and treatment cost for innovative in-hospital treatments, including those for cardiovascular (CV) diseases.
Methods: A framework was developed to analyze 30 Food and Drug Administra-

tion and/or European Medicines Agency approved in-hospital drugs and devices across multiple therapy areas, including 10 for CV diseases. Drugs and devices were only included in the study if they had shown a statistically significant mortality benefit in pivotal registration studies.
Results: For all drugs and devices included in the study, a direct correlation was observed between the patient population size and cost of treatment (R2=0.411 and 0.427 for the United States [US] and Europe, respectively) but not between the size of mortality benefit (number needed to treat [NNT]) and treatment cost (R2=0.219 and 0.101, respectively). Similarly, when only CV drugs and devices were considered, there was a correlation between the patient population size and cost of treatment in both the US (R2=0.493) and Europe (R2=0.643). A correlation between NNT and cost of treatment was also observed for CV drugs and devices, although this correlation was stronger in the US (R2=0.504) than in Europe (R2=0.359).

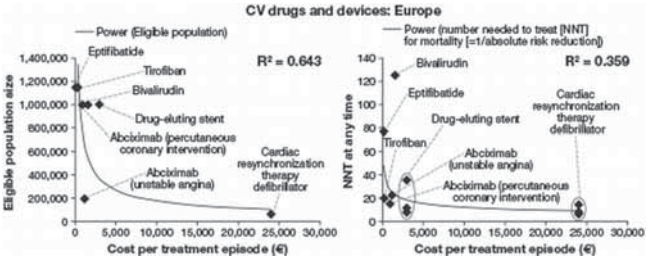

Figure 1

Conclusions: The results of this analysis provide a unique insight into factors affecting value assessments for innovative in-hospital CV treatments, and highlight that consideration of patient population size and mortality benefit, including evaluation of NNT, plays an important role.

EVOLVING INDICATIONS AND PRESCRIPTION PATTERNS IN CARDIOVASCULAR PHARMACOTHERAPY

P5879 | BEDSIDE
Comparison of carvedilol and other beta-blockers on long-term mortality in patients with acute myocardial infarction who performed percutaneous coronary intervention using drug-eluting stents

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Purpose: The use of beta-blockers is recommended for treatment of patients with acute myocardial infarction (AMI) in current guidelines. However, there was no recommendation one beta-blockers over another. The aim of this study is to compare the impact of carvedilol and other beta-blockers on long-term clinical outcome in patients with AMI who performed percutaneous coronary intervention (PCI) with drug-eluting stents (DES).
Methods: A total of 4,748 AMI patients undergoing PCI with DES were consecutively enrolled in the COREA-AMI (COnvergent REgistry of cAtholic and chonnAm university for AMI) registry from January 2004 to December 2009. Among 4,748 patients, 1,163 patients who did not prescribe any beta-blockers were excluded. We divided into two groups: carvedilol group (n=2,921) and non-carvedilol group (n=664). Non-carvedilol group included bisoprolol, atenolol, betaxolol, and nebivolol. The primary endpoint was a cardiac death during 3-year follow-up.
Results: During 3-year follow-up, the rate of cardiac death was 7.6% in carvedilol group and 10.7% in non-carvedilol group (p=0.002), respectively. In multivariate model, the use of carvedilol reduced the rate of cardiac death (adjusted HR 1.776, 95% CI 1.244-2.537, p=0.002).

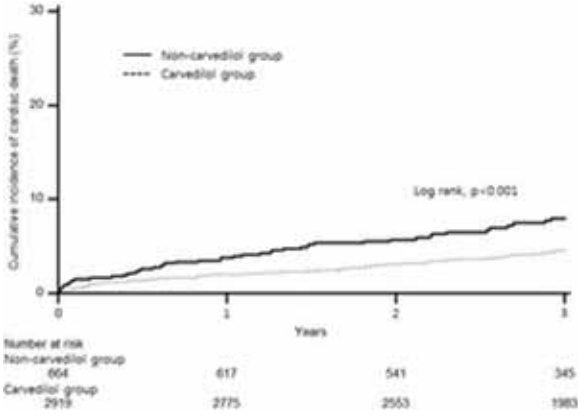

Figure 1

Conclusions: Carvedilol was associated with reduced cardiac death in patients with AMI treated with PCI using DES compared with other beta-blockers.

P5880 | BEDSIDE
Hypertensive patients treated with beta blockers prior to surgery are at increased risk of major adverse cardiovascular events and death – a nationwide cohort study

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Purpose: The safety and efficacy of continued beta blocker therapy treatment in patients with a stable condition i.e. hypertension, undergoing non-cardiac surgery, is largely unknown.
Methods: Through nationwide registers we identified hypertensive patients undergoing non-cardiac surgery using a validated algorithm (treatment with at least two antihypertensive drugs; RAS-inhibitors, beta blockers, calcium antagonists or thiazides plus no prior cardiovascular or kidney disease). The risk of 30-day MACE (non-fatal AMI, non-fatal ischemic stroke and cardiovascular death) and 30-day all-cause mortality were calculated using Cox proportional hazard models adjusted for sex, age, type of surgery and surgery risk category (low, intermediate, and high).
Results: A total of 44,506 patients were included, 33,319 received RAS-inhibitors, 13,310 received beta blocker, 25,355 received calcium antagonists, and 24,273 received thiazides. The incidence of MACE and death in the overall population were 1.29% and 1.83%, respectively. Hazard ratios (95% confidence intervals) for single antihypertensive drugs and specific drug combinations are presented in Fig. 1.

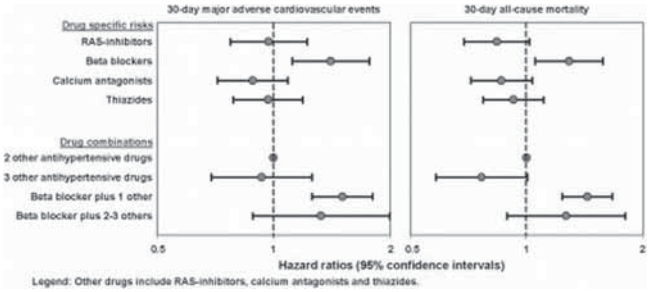

Figure 1

Conclusion: Antihypertensive treatment with beta blockers prior to surgery is associated with increased risk of perioperative adverse outcomes.

P5881 | BEDSIDE
Effectiveness of perioperative ivabradine in patients undergoing vascular surgery

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Background: Perioperative control of heart rate (HR) is important for achieving cardioprotection in high risk patients. However, effective HR control with B-blockers (BB) may be difficult to achieve and may be associated with increased risk especially when initiated <1 week before surgery.
Aim: To assess the effectiveness of ivabradine in reducing perioperative HR in patients undergoing vascular surgery.
Method: Patients scheduled for elective open vascular surgery with HR >75 bpm and revised cardiac risk index (RCRI) score >2 were prospectively enrolled. Ivabradine was given to 45 patients (Ivab group) with any of the following: inadequate HR control despite BB therapy; contraindication to BB; or surgery schedules in less than a week. Another 26 patients received titrated doses of bisoprolol according to current guidelines (standard care group). Medications were continued for 30 days postoperatively. Cardiac troponin T (cTn) was measured before surgery and on postoperative days 1, 3, and 7. Target HR was defined as <65 bpm. Thirty-day cardiac events were the composite of cTn release, death, and stroke.
Results: Both groups were similar in terms of age, RCRI score, and surgical procedure. HR was similar in both groups before therapy (86±5 vs. 85±4 beats/min) but was significantly lower in Ivab group preoperatively (64±4 vs. 71±9 beats/min, $p<0.001$) and at first postoperative day (66±8 vs. 78±12 beats/min, p=0.007) with similar rates of clinically significant hypotension or bradycardia. More patients in Ivab group than in standard care group achieved target HR (66% vs. 31%, p=0.003). Thirty-day cardiac events were higher in standard care group (37%) versus Ivab group (9%, p=0.003); this was driven mainly by excess rate of cTn release. Independent predictors of cardiac events were: RCRI score (odds ratio (OR) = 4.2, 95% confidence interval (CI): 1.8-5.7, p=0.013); lack of aspirin

use (OR = 2.7, 95%CI: 1.2-3.7, p=0.01); and HR at first postoperative day (OR = 1.2, 95% CI: 1.02-2.3, p=0.0007)
Conclusion: In high risk patients undergoing vascular surgery, perioperative ivabradine is effective in HR control and may be associated with improved post-operative outcomes.

P5882 | BENCH
The right ventricle molecular changes associated with pulmonary arterial hypertension are attenuated by neuregulin-1 treatment

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Pulmonary arterial hypertension (PAH) leads to right ventricular (RV) failure and death. Neuregulin (NRG)-1 has been implicated in several processes regulating cardiac development, as well as cardiac and vascular homeostasis. It was previously shown, in an experimental model of MCT-induced PAH, that NRG-1 treatment is able to restore PAH-induced severe abnormalities in cardiac function and structure. This study investigated the underlying molecular mechanisms to the beneficial effects of NRG-1 in myocardial function, in the same animal model of induced PAH.
Male Wistar rats randomly received monocrotaline (MCT, 60mg/kg,sc) or vehicle. After 14 days, animals received NRG-1 (40μg/kg/day,ip) or vehicle, resulting in 4 groups: CTRL; CTRL+NRG-1; MCT; MCT+NRG-1. RV sample collection for were performed 21-24 days after MCT administration. Only significant results (mean$\pm$SEM, $p<0.05$) are given.
NRG-1/ErbB system components expressions in MCT animals are changed. We observed increased levels of NRG-1 in RV (11.1$\pm$2.8 vs 1.0$\pm$0.3 AU, MCT vs CTRL), which were reversed by NRG-1 treatment (MCT+NRG-1: 0.7$\pm$0.5 AU), and decreased levels of ErbB4 in all MCT animals (MCT: 0.6$\pm$0.2 and MCT+NRG-1: 0.7$\pm$0.15 AU). We also found increased levels of ErbB2 (2.0$\pm$0.3 AU), ADAM-17 (2.1$\pm$0.3 AU) and ADAM-19 (2.7$\pm$0.3 AU), and increased eNOS expression (2.0$\pm$0.3 AU) in the RV of MCT animals that not reversed with NRG-1 treatment. MCT treatment led to altered GLUT1 expression (4.1$\pm$0.5 AU) and NRG-1 treatment attenuated this increase (1.7$\pm$0.3 AU). GLUT4 was increased in all animals treated with NRG-1 (CTRL+NRG-1: 1.4$\pm$0.1; MCT+NRG-1: 1.5$\pm$0.2 AU). Increased RV caspase 3 (MCT: 4.4$\pm$0.4 AU) and plasmatic expression of IL-6 and TNF-α (IL6: 2.7$\pm$0.7 AU; TNF-α: 1.7$\pm$0.3 AU) were attenuated by NRG-1 treatment (caspase 3: 1.7$\pm$0.3 AU; IL6: 2.0$\pm$0.4 AU; TNF-α: 1.5$\pm$0.4 AU). Moreover, we found that the increased expression of BNP (17.5$\pm$2.2 AU), ET-1 (5.0$\pm$1.2 AU) and HIF-1α (4.3$\pm$1.1 AU) observed in MCT animals was attenuated or reversed with NRG-1 therapy (MCT+NRG-1: 5.6$\pm$1.9; 1.7$\pm$0.7; 1.4$\pm$0.1 AU, respectively).
In conclusion, we show that NRG-1 treatment is able to restore the changes in expression of markers of cardiac overload, hypertrophy and hypoxia induced by PAH. These beneficial effects of NRG-1 are associated with the modulation of different signaling pathways, namely apoptotic, metabolic, survival/ proliferation, and inflammation pathways.

P5883 | BEDSIDE
Ivabradine in pulmonary arterial hypertension

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Background: Pulmonary arterial hypertension (PAH) is a disabling chronic disorder of the pulmonary vasculature, which is characterized by increased pulmonary artery pressure as a result of increased pulmonary vascular resistance. We therefore sought and verify clinical differences between PAH patients in ivabradine treatment vs controls and verify a possible functional improvement after ivabradine treatment.
Methods: Between 1st July 2009 and 1st July 2013, a total of 28 consecutive outpatients with PAH in specific therapy were evaluated in our ambulatory for diagnosis and treatment of PAH. Non-invasive cardiac evaluation included: clinical evaluation, ECG, and echocardiography, with estimation of the PAsP. Functional capacity was assessed through six minute walking test (6MWT). Finally, RHC was required to confirm the diagnosis of PAH. Ivabradine, a selective inhibitor of the sinus node If channels, was added to all patients with a HR over 100 bpm or symptomatic for palpitations. Clinical follow up was performed every 6 months for a mean 452$\pm$322 days mean follow up. Clinical follow up was anticipated in case of worsening conditions.
Results: 28 PAH patients undertaken specific drugs for PAH; Patients treated with ivabradine were older (65$\pm$13 vs 59$\pm$14, p: NS) and characterized by higher values of HR (90,3$\pm$10 bpm vs 73$\pm$11 bpm, p: 0,001), higher incidence of SSc-PA (40% vs 22%, p: NS), higher incidence of combination therapy (60% vs 11%, p: 0,005), higher rates of in III-IV NYHA functional class (80% vs 61%, p: NS). No hemodynamic difference was observed, (PAsP: 69.3$\pm$30.2 mmHg vs 70.2$\pm$24.6, p: NS; mPAP: 40.3$\pm$12.09 mmHg vs 37,83$\pm$19,15, p: NS). After long-term therapy with ivabradine, the patients improved their functional status (6MWT: 299 m vs 354 m, p: 0,038), and did not complain of palpitations anymore. They were followed for a mean 452$\pm$322 days mean follow up. Only for one patient, with congenital heart disease (CHD) and in treatment with iloprost and ambrisentan there was discontinuation of the ivabradine without specific symptomatology; the same patients have already suppressed digoxin, sildenafil and tadalafil.
Conclusions: Our preliminary data show that patients who could benefit most from ivabradine are those older, with higher HR, SSc-PA, already in combination therapy, and in III-IV NYHA functional class. Further studies in larger cohorts of patients and randomized trials, however, are needed to confirm these preliminary results.

P5884 | BEDSIDE
Prescribers practice of assessing arrhythmia risk with QT-prolonging medications

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Purpose: Acquired QTc prolongation from drug therapy is well known. Such drugs are widely prescribed and their pro-arrhythmic risks are often under recognised. This study aimed to assess prescribers' monitoring for arrhythmic risk with QT-prolonging medications (LQT drugs).
Methods: Over a 6-month period, all inpatients under the care of Cardiologists (Cohort A) and General Internal Physicians (Cohort B) at Aberdeen Royal Infirmary prescribed LQT drugs were identified. Only drugs with known risk of Torsades de Pointes (TdP) defined by The Arizona CERT website were studied. Admission and repeat electrocardiograms (ECG) after 48 hours of commencing a LQT drug were examined. Actions taken if QTc was prolonged were identified and drug-drug interaction examined. The results were extrapolated to estimate the risk of TdP from LQT drugs to the UK hospital population.
Results: Of the 4133 patients admitted during the study period, 234 patients were prescribed a LQT drug (100 in Cohort A and 134 in Cohort B).
Of those (75%) admitted with a pre-existing LQT drug prescription, an ECG was performed in all patients in Cohort A and 93% in cohort B. A combined total of 34% in this subgroup had a prolonged QTc. Of those (25%) who received a new prescription of LQT drug, significantly more patients in Cohort A had a repeat ECG within 48 hours of commencing a LQT drug compared to Cohort B (84% vs. 11%, $p<0.0001$). Only 6 patients (14%) in Cohort A and 2 patients (5%) in Cohort B with a prolonged QTc were recognised as such by their clinicians. The LQT drug was stopped in one patient from each cohort. Primary care physicians were notified of QTc prolongation in 2 cases. Sixteen patients (7%) across both cohorts were on two LQT drugs. Only one patient at risk of drug interaction had QTc prolongation.
Observed rates of TdP with antiarrhythmics are thought to be >1% and non-cardiac drugs between <0.01% and 0.1%; none of our patients had documented TdP in hospital. Extrapolating our study findings to the UK hospital population, we estimate that at least 204 and between <17 and 175 patients on cardiac and non-cardiac LQT drugs respectively might be expected to have TdP.
Conclusion: Recognition of acquired QTc prolongation is poor. Clinician education and/or an electronic prescribing system may improve this situation.

P5885 | SPOTLIGHT
Quality of assessment process and counseling provided to cardiac patients by community pharmacists: a simulated-client study

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Purpose: Easy access to pharmacies and self-medication is common in our country. The interaction of pharmacists with cardiac patients and their counseling in is unknown. In this study we sought to explore how pharmacists interact and counsel cardiac patients.
Methods: A total of 600 community pharmacies in the two large cities were randomly selected and stratified by the region, and time of the day and week. Two investigators visited each pharmacy and simulated having a parent with either chest

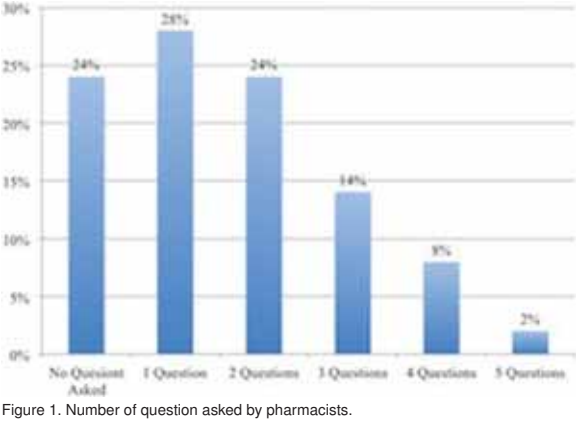

Figure 1. Number of question asked by pharmacists.

pain for the acute coronary syndrome (ACS) scenario or shortness of breath for acute heart failure (AHF) scenario. Further information was provided only if asked for by the pharmacist. The other investigator observed the conversation and after each visit collect the data using standardized data collection form.
Results: Of 600 pharmacies, 380 (63.3%) pharmacists advised the simulated patient to seek medical care, more so with the ACS scenario (70.3% vs. 56.3%, p<0.001). The pharmacists were likely to advice patients to seek medical advice during weekdays than weekends, and during the morning hours than during the evenings or nights. Pharmacists sought more information regarding other symptoms and comorbidities with the simulated ACS patients (59.7% vs. 48.7%, p=0.009 and 46.3% vs. 37.3%, p=0.031 respectively). Only 28 pharmacists (4.7%) inquired about drug allergies and 14.3% gave instructions on treatment duration, with no significant differences between the two scenarios.
Conclusions: Assessment of simulated cardiac patients by community pharmacists was inadequate and the quality of provided counseling is extremely suboptimal. This indicates the need for the implementation of major practice changes to improve the quality of service provided to cardiac patients by community pharmacists.

ENDOTHELIAL CELL FUNCTION: BEDSIDE TO BENCH

P5886 | BEDSIDE
Dietary nitrate improves endothelial function, vascular stiffness and modifies platelet markers of atherogenesis in hypercholesterolemia

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Purpose: Recent evidence suggests that orally ingested inorganic nitrate undergoes sequential chemical reduction in vivo first to nitrite and then to nitric oxide (NO) within the circulation. The provision of NO within the vasculature improves platelet and endothelial reactivity in healthy volunteers. We sought to examine whether dietary nitrate might be effective in improving endothelial and platelet function in a cohort at risk of cardiovascular disease ie. hypercholesterolemics.
Methods: 67 otherwise healthy non-diabetic untreated hypercholesterolemics completed this randomised double blind placebo controlled parallel study of a once daily dietary nitrate dose for 6 weeks (n=33, Nitrate rich beetroot juice, 250 ml of 24.1±7.7mM) vs Placebo (n=34, nitrate-depleted juice, 250 ml of 0.05±0.1mM). The primary end point was endothelial function determined using ultrasound flow-mediated dilation (FMD) at baseline and at 6 weeks. Pulse wave analysis (PWA) and pulse wave velocity (PWV) were also measured and blood taken for assessment of plasma cholesterol, platelet P-selectin expression and platelet monocyte aggregate (PMA) formation using flow cytometry. Plasma, urine and salivary nitrate and nitrite measurements were conducted using ozone chemiluminescence. Values shown are mean±SEM.
Results: Plasma levels of nitrate increased ~8-fold from a baseline of 26.7±2.3 μM (p<0.0001) and nitrite 2.5-fold from 0.3±0.1μM (p<0.0001) in the Nitrate limb, whilst no changes occurred in the Placebo limb. LDL cholesterol was similar at baseline between the groups with a non-significant trend to reduction in the Nitrate limb (Nitrate: 4.5±0.7 to 4.2±1.0 mmol/L, Placebo: 4.4±0.9 to 4.4±0.9 mmol/L). FMD increased by ~24% in the Nitrate limb (4.6±0.4% to 5.7±0.5% p<0.001) vs a trend to decrease in the Placebo group (4.5±0.3% vs 4.3±0.3% p=0.07). A small improvement in PWV (8.3±0.2 to 8.1±0.2m/s, p=0.02) and PWA augmentation index (28.7±1.2 to 26.4±1.3 m/s, p=0.04) was noted in the Nitrate limb with non-significant increases in the Placebo. PMA formation was reduced in the Nitrate limb by 10.0±3.9% vs an increase of 5.2±3.6% in the Placebo group (p=0.007). Platelet P-selectin expression trended to reduction in the Nitrate limb but this was non-significant (Nitrate limb: 0.8±0.2 to 0.4±0.09%, Placebo: 0.6±0.2 to 0.7±0.2%).
Conclusions: Once daily dietary nitrate ingestion improves endothelial function, vascular stiffness and platelet markers of atherogenesis in hypercholesterolemics. Dietary nitrate may be useful as a potential preventative strategy in the battle against atherogenesis.

P5887 | BEDSIDE
The role of vascular function in patients with diabetic retinopathy

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Purpose: Diabetic Retinopathy (DR) is a complication of diabetes mellitus and remains a leading cause of irreversible blindness. Measurement of endothelial function and arterial stiffness are well validated in large population studies as strong predictor of adverse cardiovascular outcomes. We investigated the possible association of DR with endothelial function, arterial stiffness and inflammation.
Methods: We enrolled 100 consecutive subjects with DR (mean age 69±9 years), 100 consecutive subjects with diabetes but no evidence of DR (NDR) (mean age 64±10 years) and 100 healthy subjects (mean age 63±11 years). Endothelial function was evaluated by flow mediated dilation (FMD) in the brachial artery, carotid-femoral pulse wave velocity (PWV) was measured as an index of arterial stiffness and augmentation index (AIx) as an index of reflected waves. Creatinine clearance, glycosylated hemoglobin, and C reactive protein were measured.
Results: Patients with DR compared to NDR patients and healthy subjects had impaired FMD (3.55±1.23% vs. 5.71±1.92% vs. 7.54±3.06%, p<0.001), increased PWV (11.06±2.75m/sec vs. 9.16±1.97m/sec vs. 8.41±1.75m/sec, p<0.001) and increased AIx (27.85±8.15% vs. 24.12±7.96% vs. 22.52±8.00%, p<0.001). In diabetic patients, we applied a forward logistic regression model, which revealed that impaired FMD was the strongest predictor of the presence of DR [Odds ratio=0.34, 95%CI (0.23, 0.51), p<0.001]. As many confounders may exists, we applied a second logistic regression model which revealed that impaired FMD was independently associated with the presence of DR [Odds ratio=0.17, 95%CI (0.074, 0.394), p<0.001] even after adjustments for confounders such as sex, age, glycosylated hemoglobin and C reactive protein levels, duration of diabetes, body mass index, type of treatment and the presence of arterial hypertension and dyslipedemia. Moreover, among diabetes mellitus patients ROC curve analysis revealed that FMD has sufficient discriminate ability to detect DR (AUC=0.85, 95%CI 0.80 to 0.91, p<0.001) and an FMD value below 4.35% has a sensitivity of 82%, and a specificity of 79% for the diagnosis of DR. Importantly, the negative predictive value of an FMD above 4.36% was estimated at 85%.
Conclusion: This study showed that DR patients have significantly impaired endothelial function and increased arterial stiffness compared to NDR patients and to healthy people. Importantly, impaired FMD is strongly and independently associated with the occurrence of DR highlighting the role of dysfunctional endothelium in the progression of microvascular diabetic complications.

P5888 | BEDSIDE
Adaptive immune responses and endothelial function in young adult survivors of childhood acute lymphoblastic leukemia

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Purpose: Adult survivors of childhood malignancy are at increased risk of early atherosclerosis and late cardiovascular complications. Innate and adaptive immune mechanisms play an important role in atherogenesis. Macrophages and effector T cells produce proinflammatory mediators and contribute to the progression of atherosclerotic plaques. The aim of the study was to assess endothelial function and T lymphocytes subsets in young adult survivors of childhood acute lymphoblastic leukemia (ALL).
Methods: We examined 27 (age 18-28, median 20) ALL survivors who had completed chemotherapy at least 5 years prior to the study and 20 healthy controls. Endothelial function was assessed using flow mediated dilation (FMD) of brachial artery. Flow cytometry was used to identify naive, central memory, effector memory and effector T cells among CD4+ and CD8+ subsets of lymphocytes.
Results: FMD (5.3±6.7 patients vs 6.1±4.6% controls; p=0.71) and common cardiovascular risk factors were comparable except for lower HDL cholesterol (1.5±0.4 vs 1.8±0.5 mmol/l; p=0.02) in the study group. ALL survivors had lower levels of total CD4+ T cells (631±166/ul vs 758±249/ul; p=0.048), which was dependent on decreased numbers of naive CD4+ T cells compared with healthy controls (260±125/ul vs 353±153/ul; p=0.02). Central memory, effector memory and effector CD4+ T cells were similar in both groups as well as total CD8+ and CD8+ lymphocyte subsets. Of note, in ALL survivors but not in the controls numbers of CD4+ T cells (r=0.51; p<0.05), memory CD4+ T cells (r=0.46; p<0.05) and central memory CD4+ T cells (r=0.53; p<0.05) were correlated with FMD. No significant correlations were observed between other T cell subpopulations, FMD and common CVD risk factors including blood pressure, lipids and BMI.
Conclusions: Adaptive immune dysfunction reflected by lower levels of CD4+ T cells was present in ALL survivors and associated with the magnitude of endothelial dysfunction as assessed by flow mediated dilation. Decreased naive helper T lymphocytes may result from enhanced differentiation of naive T cells into effector T cells which migrate from the blood into intima and participate in the maintenance of chronic inflammatory responses within the vascular wall, which might contribute to endothelial dysfunction on a long-term basis.

P5889 | BENCH
Premature coronary artery disease is associated with vascular and endothelial cell dysfunction

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Background: Patients with a family history of coronary artery disease (CAD) have an increased risk of early-onset, diffuse atherosclerosis. The mechanisms that underpin this association are only partly understood. We hypothesise that

inadequate vascular repair mechanisms predispose to atherosclerosis in patients with a family history of CAD compared to age- and sex-matched controls.
Methods: Sixteen patients (51±5 years; 94% male) with premature CAD (<50 years old) and a family history of CAD (first degree relative) and 16 healthy, age- and sex-matched controls (50±6 years) with normal coronary arteries underwent a detailed assessment of vascular function. Bilateral forearm blood flow was measured before and during unilateral intra-brachial arterial infusion of acetylcholine (5 - 20 μg/min) and sodium nitroprusside (2 - 8 μg/min). Vascular endothelial cells were isolated and cultured from venous biopsies of superficial forearm veins and from peripheral blood mononuclear cells. Endothelial progenitor cells (EPCs) were quantified in whole blood as CD34+CD133+KDR+ subpopulations and both vascular- and circulating mononuclear cell-derived endothelial outgrowth cells (EOCs) were characterized by flow cytometry, immunocytochemistry and by cell adhesion and wound healing assays in-vitro.
Results: Endothelial-dependent vasodilation was impaired in patients with premature CAD compared to controls (P=0.03) but endothelial-independent vasodilatation was unchanged (P=0.37). There were no differences in the number of CD34+, CD34+CD133+, or CD34+CD133+KDR+ cells in blood between patients and controls, but endothelial outgrowth appeared later in patients (patients vs. controls = 10.30±0.81 vs. 7.94±0.54 days; P=0.03). The level of CD133 expression on vascular EOCs was reduced in patients compared to controls (P=0.001). Vascular EOCs from patients displayed reduced adhesion to collagen compared to vascular EOCs in controls (P=0.02). Migration of vascular EOCs was reduced compared to circulating EOCs in patients (% coverage 24 hrs = 35.94±8.8 vs. 62.22±8.2, P=0.04). No differences were observed in the migration of vascular EOCs compared to circulating EOCs in controls (% coverage 24 hrs = 64.81±12.7 vs. 56.25±8.0; P=0.56).
Conclusion: Patients with premature CAD and a family history of CAD have deficiencies in both endothelial vasomotor function and in the proliferation, adhesion and migration of vascular and circulating endothelial cells. These mechanisms suggest the genetic basis of premature CAD may be mediated in part by inherited defects in endothelial function and vascular repair.

P5890 | BENCH
Association between NADPH oxidase activity and NO bioavailability in atherosclerotic plaques

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Purpose: Oxidative stress and the generation of reactive oxygen species (ROS), including superoxide (O2-) are thought to play a critical role in pathophysiology of atherosclerosis. NADPH oxidase and eNOS synthase may be considered as the pivotal sources of ROS contributing to a decreased NO bioavailability in the endothelium, leading to endothelial dysfunction. This study was established to determine whether NADPH oxidase-derived O2- can contribute to a decrease production of bioactive NO by eNOS in the endothelium overlaying the arterial atherosclerotic plaques.
Methods: The endothelial cells, that were harvested from atherosclerotic and non-atherosclerotic (control tissue) regions of carotid arteries isolated from patients scheduled to carotid trans-endarterectomy, were used for further investigation. The protein expression of NADPH oxidase subunits (NOX 4 and p47phox) was analyzed by Western blot technique. The NADPH oxidase activity was measured with lucigenin (5 μmol/L)-based assay for O2- production. Concurrent kinetics of NO, O2- and ONOO- radicals releases from single endothelial cells were measured with highly sensitive electrochemical nanosensors.
Results: The reduced release of NO (556 vs. 214 nmol/L) with simultaneous increased releases of both O2- (21 vs. 71 nmol/L) and ONOO- (288 vs. 648 nmol/L) were observed in endothelium from atherosclerotic arteries in comparison to control tissue. Moreover, in comparison to control, the endothelial cells overlaying the atherosclerotic plaques revealed a significant increase of NADPH oxidase activity (0.27±0.05 vs. 0.14±0.03 RLU/min/mg) as well as an increased expression of total and membrane fractions of p47phox subunit. The NOX4 subunit expression showed no differences in total and membrane-bound fractions of the endothelial cells retrieved from atherosclerotic and non-atherosclerotic regions of the arteries.
Conclusion: We have provided the direct evidence that a reduction of NO bioavailability in the endothelium overlaying in the human atherosclerotic plaques is due to the elevated O2- production by over expressed NADPH oxidase. Reaction between NO derived from eNOS and O2- derived from NADPH oxidase is responsible for ONOO- overproduction in the endothelium of atherosclerotic plaques.

P5891 | BENCH
In vivo vascular function assessment in living mice using high resolution ultrasound: a translational model

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Background: Endothelial function is a key aspect of human vascular physiology and cardiovascular disease. Here, we present the validation of a translational animal model allowing the longitudinal study of conduit artery flow-mediated vasodilation analogous to the methodology used in human clinical studies.
Methods and results: High resolution animal Duplex ultrasound (Visualsonics) allows a simple imaging of the femoral artery in living mice. Similar to humans, distal hindlimb occlusion via an inflatable cuff is used to induce reactive hyperemia and shear stress of the upstream femoral artery. The increase in shear leads to endothelial nitric oxide synthase (eNOS) dependent vasodilation that is semi-automatically quantitated. Testing 1, 3, 5, and 10 min hindlimb occlusion protocols with and without NOS inhibition by L-NAME, we identified that the maximally achievable, almost entirely NOS-dependent vasodilation occurs at 60 sec after cuff release following a 5 min occlusion protocol. Interestingly, a NOS independent component of FMD could be detected late during reactive hyperemia starting at 90 sec of reperfusion and lasting up to 3 min and even earlier when a 10 min occlusion protocol was employed. These results and intra- and inter-observer variabilities were similar to human FMD physiology and therefore, all consecutive FMD measurements were performed using the 5 min occlusion protocol and FMD measurements taken at 60 sec of reperfusion. This response was completely abolished by L-NAME and in eNOS-KO mice. COX inhibition by indomethacine, arginase inhibition with nor-NOHA, and endothelium-derived hyperpolarizing factor inhibition by sulfaphenozole had no effect on FMD. Further validating our approach, we showed that eNOS-dependent FMD was age-dependently decreased, whereas the eNOS-independent component of FMD as assessed after L-NAME infusion remained unaffected. In ApoE-KO mice, an established accelerated atherosclerosis model, FMD measured weekly, progressively decreased upon initiation of a high cholesterol diet along with an increase in pulse wave velocity and aortic collagen content, confirming progressive arteriosclerosis.
Conclusion: This model promises to allow longitudinal studies on eNOS-dependent endothelial function in mouse models that can be directly translated to humans as the methodology is almost identical with the clinical read-out.

P5892 | BENCH
Lack of angiopoietin like-2 protects against angiotensin II-induced endothelial dysfunction in mice

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Cardiovascular diseases are characterized by chronic low-grade inflammation, oxidative stress and endothelial dysfunction. Angiopoietin like-2 (angptl2) is a recently identified pro-inflammatory protein that is elevated in atherosclerotic patients, but knowledge on its role in regulating endothelial function in a pro-inflammatory and pro-oxidative environment is limited.
Purpose: To test the hypothesis that lowering levels of angptl2 improves endothelial cell stress resistance and prevents endothelial dysfunction induced by a subpressor dose of angiotensin II (angII).
Methods: Chronic subcutaneous infusion of angII (200 ng/kg/min; osmotic minipump), or saline, was performed for 14 days in 22-week-old angptl2 knock-down (KD, n=10) mice and wild-type littermates (WT, n=10). Endothelial function was evaluated in the cerebral arteries and aorta by monitoring acetylcholine (ACh)-induced vasodilation in a pressurized arteriograph and wire myograph, respectively.
Results: In cerebral arteries of saline-treated KD and WT mice, ACh-induced vasodilation were similar; however, while dilation depended on eNOS activation in both groups (inhibited by L-NNA), eNOS-derived H2O2 (sensitive to PEG-catalase) contributed to vasodilation in WT, and only eNOS-derived NO (P<0.001) was involved in KD mice. In contrast, in the aorta of saline-treated mice, the main vasodilator NO contributed similarly in both KD and WT mice. AngII induced endothelial dysfunction in cerebral arteries of WT mice only (P<0.01), evidenced by a 60% reduction in maximal dilation induced by ACh. The impaired dilation was reversed (P<0.05) acutely by the antioxidant N-acetylcysteine (10 μM), apocynin (10 μM), a non-selective NADPH oxidase (NOX) inhibitor, or indomethacin (10 μM), a non-selective cyclooxygenase inhibitor. Global endothelial function was maintained in the aorta after angII infusion in all groups; however, angII infusion revealed prostacyclin-mediated relaxation in KD (P<0.01) but not in WT mice. Finally, in angII-treated KD mice only, apocynin significantly blunted relaxation in both the cerebral arteries and aorta (P<0.01) suggesting a global remodelling of the NOX systems, possibly by revealing the protective role of NOX4, an isoform that produces predominantly H2O2 in mediating relaxation.
Conclusions: Lack of angptl2, as shown in KD mice, protects against angII-induced endothelial dysfunction; it favours the production of NO and prostacyclin, likely increasing endothelial cell resistance to oxidative stress and maintaining relaxation, while recruiting a potential compensatory dilatory NOX pathway.

DIASTOLOGY AND IMAGING

P5893 | BEDSIDE
Emptying velocity of left atrial appendage in sinus rhythm better correlates with the veolocity of late diastolic mitral annular motion than mitral inflow

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Background: Emptying velocity of left atrial appendage (LAAeV) is well known to reflect the function of left atrium as well as LAA. We arbitrarily have used the velocity of late diastolic mitral inflow (A) as a marker of effective left atrial contraction after treatments of atrial fibrillation instead of LAAeV measured by transesophageal echocardiography (TEE). We sought to test the correlation between conventional parameters of left ventricular diastolic function and LAAeV in sinus rhythm (SR).
Methods: We studied 63 consecutive patients (23 women, mean age 60.2±13.5 years) in SR referred for the evaluation of stroke. Peak LAAeV was measured by pulsed-wave Doppler interrogation at the orifice of LAA during TEE. Parameters of left ventricular diastolic function as well as left atrial volume were measured by transthoracic echocardiography just before TEE.
Results: LAAeV could be measured in all patients with sinus rhythm (67.3±19.2 cm/s, range 13-108 cm/s). E wave (R=-0.291, p=0.024), E/e' (R=-0.346, p=0.0067) and a' (9.1±2.2 cm/s, R=0.408, p=0.0013) showed significant correlation with peak LAAeV. The velocity of A wave did not showed significant correlation with LAAeV (75.2±25.1, R=-0.074, p=0.58) (Fig. 1). LAAeV showed fair correlation with LA dimension (R=-0.495, p<0.0001) and LA volume (R=-0.482, p=0.0001). In multiple regression, a' and LA dimension were significant determinants of LAAeV (p=0.0088 and 0.0011, respectively).

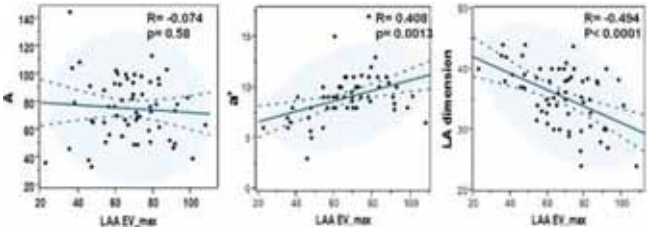

Figure 1

Conclusions: Peak LAAeV in SR fairly correlated with parameters of left ventricular diastolic function. Decreased LAAeV significantly correlated with increased LA dimension and the velocity of a', but unexpectedly not with the velocity of A wave. Thus a' wave rather than A wave might be a more reliable surrogate for LAAeV in patients with restored SR.

P5894 | BENCH
Systolic and diastolic biventricular function in systemic sclerosis: a 3-year longitudinal study

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Objectives: To investigate by standard echocardiography (SE) and pulsed tissue Doppler imaging (TDI) the course of systemic sclerosis (SSc) - heart disease (HD) and its correlation with epidemiological, clinical and serological features of the disease and drug treatment.
Methods: Seventy-four consecutive patients with SSc (69 female, aged 19-71 years, disease duration 1-43 years) and 71 age- and sex-matched controls underwent cardiac assessment at baseline and at 3-year follow-up.
Results: At baseline, SSc patients showed an impaired left (LV) and right ventricular (RV) diastolic function compared to controls (Em/Am 0.85±0.4 vs 1.5±0.7, p=0.000001; Et/At 0.9±0.3 vs 1.3±0.4, p=0.000001) and subtle LV and RV systolic dysfunction (Sm 13.7±2.7 vs 15.4±3.2 cm/sec, p=0.001; St 14.4±3.5 vs 15.7±4.7 cm/sec, p=0.03). Pulmonary artery systolic pressure (sPAP) was significantly higher in SSc patients than in controls (26.1±6.0 vs 24.1±5.1; p=0.0013). At 3-year follow-up, SSc patients showed a further deterioration of biventricular diastolic and systolic function and a further increase in sPAP. At multiple regression analysis of baseline data, Em/Am <1, detected in 55/74 SSc patients vs 25/71 controls (p<0.0001), was associated with age >40 years (p=0.0001), and Et/At <1, detected in 16/74 patients vs 7/71 controls (p<0.0001), was associated with NYHA class ≥II (p=0.018), late capillaroscopic pattern (p=0.022) and a Medsger severity score ≥1 (p=0.0459). TDI evidence of new abnormalities in RV and/or LV diastolic function was associated with a Medsger severity score ≥1 (p=0.01). No correlation was observed between diastolic or systolic abnormalities or sPAP changes and drug treatment.
Conclusions: Our study confirms that SSc patients exhibit biventricular systolic and diastolic dysfunction and increased sPAP, with a further deterioration at 3-year follow-up, and suggests that currently available drugs have no protective effect on the course of SSc-HD.

P5895 | BEDSIDE
Relation of presence and severity of metabolic syndrome with left atrial mechanics in patients, a deformation imaging study

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Objective: We aimed to investigate left atrium (LA) function by speckle tracking echocardiography in women with metabolic syndrome (MetSyn) admitted in chest pain unity with normal coronary angiography and to show a possible relationship between the severity of MetSyn and LA function
Methods: We included 180 MetSyn patients without diabetes and 50 controls. The patients were classified into three groups based on the number of MetSyn criteria. The peak LA strain at the end of the ventricular systole (LAs-strain) as well as the LA strain with LA contraction (LAa-strain) was obtained. Correlation analysis performed to assess the association of LA strain parameters with the severity of MetSyn and logistic regression analysis performed to assess the relationship of low LA strain with MetSynd
Results: Both LAs (33.5±6.7 vs. 24.3±11.2, p<0.01) and LAa (20.4±4.2 vs. 13.0±6.4, p<0.001) strain measurements were found to be significantly decreased in patients with MetSyn when compared to the control group. Moreover, both LAs and LAa were found to be significantly decreased with the increasing severity of the MetSyn. A multiple logistic regression analysis demonstrated that the presence of MetSyn [OR: 0.34 (95% CI 0.04-0.89), p=0.032] and left ventricular ejection fraction [OR: 1.23 (95% CI 1.02-1.77), p=0.03] were independent predictors of LAs strain.
Conclusion: MetSyn is associated with reduced LAs strain and LAa strain representing LA reservoir and pump function, respectively. Furthermore, LA mechanical function decreases even more with the increasing severity of the MetSyn.

P5896 | BEDSIDE
Is there a relation between left ventricular diastolic elastance and end-systolic elastance?

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Background: The ratio of mitral inflow and annular velocity to stroke volume (E/e'/SV) has been reported as an index of diastolic elastance (Ed). However, its relation to end-systolic elastance (Ees) arterial elastance (Ea) and ventricular-arterial coupling (VAC); the ratio of Ea to Ees, still has not been assessed. Our aim was to assess if Ed is related to VAC and its major components.
Methods: We studied 54 normal subjects (mean age 35±12.3 years, 54% males). Diastolic functional parameters including mitral inflow early (E) and late (A) velocities, E/A ratio, mitral annular early (e') diastolic velocities, E/e', pulmonary vein inflow systolic (S) and diastolic (D) velocities and systolic pulmonary artery pressure (SPAP) were measured. Ea was approximated by the ratio of end-systolic pressure (ESP) to SV. Ees calculated as the ratio of ESP to end-systolic volume and ventricular-arterial coupling defined as the ratio of Ea/Ees.
Results: The mean values of Ea, Ees, Ed and ventricular-arterial coupling (all adjusted for body size) were higher in females. Ea, Ed and VAC were related to age (r= -0.35, 0.47 and 0.42 respectively), but Ees was not (r=-0.21). Ed was related to Ea (r=0.89) and VAC (r=-0.67) but not to Ees (r=-0.15). These relations were more prominent in females than in males (r=0.87 versus r=0.91 and r=0.54 versus r=0.77 respectively, all P<0.05).

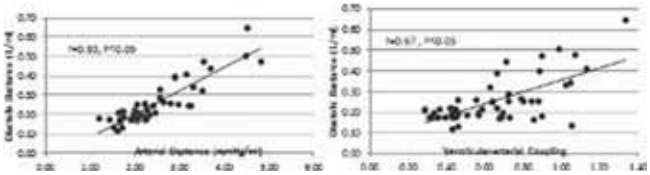
Figure 1

Conclusion: In normal subjects diastolic elastance is related to arterial elastance and ventricular-arterial coupling, but not to ventricular elastance, and this relation is more noticeable in females.

P5897 | BEDSIDE
Left ventricular dysfunction compromises proportionally left atrial filling during systole

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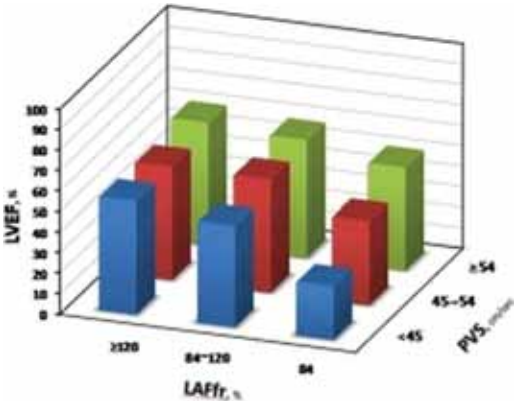
Purpose: Left atrial (LA) reservoir function is the main determinant of left ventricular (LV) stroke volume as well as LV filling. Several factors may affect LA filling such as LA relaxation function, LV contraction through the descent of the base during systole, LA chamber stiffness, and right ventricular systole through pulmonary venous inflow. We sought to investigate the impact of LV systolic function on LA reservoir function.

Methods: One hundred sixty-three consecutive patients (M:F = 101:62, age = 56±15 years, LVEF = 49±15%) who underwent 2D echocardiography were enrolled. Patients with moderate to severe mitral regurgitation, mitral stenosis or atrial fibrillation were excluded. LA minimum (LA volume at LV end-diastole, LAVmin) and maximum (LA volume at LV end-systole, LAVmax) volumes were measured using biplane disc method. LA reservoir function was estimated by calculating LA filling fraction (LAFfr) during LV systolic period; LAFfr = 100 × (LAVmax – LAVmin)/LAVmin. Peak velocity of pulmonary vein systolic flow (PVS) was also measured.
Results: LAFfr showed a strongly positive correlation with LVEF (r=0.734, p<0.001) and also showed significant correlations with both LVMI and E/e' (r= -0.569, p<0.001; r= -0.534, p<0.001, respectively). And LVEF was strongly correlated with PVS (r=0.639, p<0.001). In a multivariate regression analysis, LVEF resulted to be a strong significant predictor of LAFfr (β=0.593, p<0.001) and PVS (β=0.646, p<0.001).



Relations of LVEF to LAFfr and PVS.

Conclusions: Our data supports that LV systolic function which influences LA enlargement and subsequent LA stretching might be a strong determinant of LA filling reservoir function during systole. LV dysfunction which is proportionally compromising LA reservoir function may be one of important contributing factors of LV filling impairment.

P5898 | BEDSIDE
Synergistic effects of left atrial deformation and left ventricular diastolic function on physical fitness in elderly men

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Background: Both atrial function and ventricular diastolic function are important in exercise performance. However, the interactions between left atrial (LA) and left ventricle (LV) diastolic function on functional capacity have never been studied. We studied the influences of both LA function and LV diastolic function on physical capacity in elderly.
Methods: We recruited 269 community-based, apparently healthy elderly men who were 65 years and older (mean age 74±6 years) without structural heart disease. LA function was evaluated by 2-dimensional speckle tracking echocardiography. Average peak systolic strain of LA (LAS) during atrial filling was used as index for LA function. The ratio of peak early filling velocity (E) of mitral inflow to average early diastolic annulus velocity (e') of the annulus (E/e') was used as index for LV diastolic function. Physical capacity was assessed by 2 methods including time for 15-foot walking test and time for 8-foot up-and-go test.
Results: Time for 15-foot walking test was significant correlated with age (r=0.287, p<0.001), E/e' (r=0.208, p<0.001), biplane left ventricular ejection fraction (EF) (r = -0.155, p=0.016), and LAS (r = -0.230, p<0.001). Time for 8-foot up-and-go test was significant correlated with age (r=0.265, p<0.001), E/e' (r=0.224, p<0.001), and LAS (r = -0.268, p<0.001). Multivariate regression analysis showed age (B = 0.278), E/e' (B = 0.229), LAS (B = -0.207), and EF (B = -0.159) were independent factors for 15-foot walking test. Age (B = 0.227), E/e' (B = 0.238), and LAS (B = -0.199) were independent factors for 8-foot up-and-go test. We further divided subjects into two groups according to LV diastolic function or median level of LAS. Subjects with both impaired LV diastolic function (E/e' >8) and lower LAS (LAS <38.2%) had the poorest functional capacity than subjects with normal LV diastolic function and higher LAS represented by time for 15-foot walking test (5.9±2.4 vs. 4.7±1.3 sec, p=0.003) or time for 8-foot up-and-go test (10.1±5.4 vs. 7.5±2.0 sec, p<0.001).
Conclusion: Both LA function and LV diastolic function are independently correlated with time for 15-foot walking or 8-foot up-and-go tests. They have synergistic effects on physical fitness in elderly men.

P5899 | BEDSIDE
Left ventricular strain and ventricular-arterial coupling in heart failure with preserver ejection fraction: results from ICAS-HF registry

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Background: Ventricular-arterial (VA) coupling has reported to have the critical role in heart failure with preserved ejection fraction (HFpEF), however, its association with left ventricular (LV) global longitudinal strain (GLS) and left ventricular (LV) circumferential strain (GCS) is still uncertain in clinical setting.
Methods: Among 457 heart failure patients who require hospitalization were analyzed from ICAS-HF (Ibaraki Cardiovascular Assessment Study for Heart Failure) multi-center registry, 141 patients (mean age 75±10 years, male 54%) with left ventricular ejection fraction over 50% at the discharge were divided into two groups according to the median value of GLS of -15%. VA coupling was defined as the ratio of LV end-systolic volume to stroke volume by echocardiography.
Results: The demographic and clinical characteristics showed no significant difference between GLS<-15% and GLS>-15% groups as follows; age 78±7, 73±11 years, systolic blood pressure 127±19, 118±20 mmHg, LVEF 62±8, 58±7%, BNP 235±220, 302±343pg/mL, respectively. But, GCS had markedly deteriorated in impaired GLS (<-15%) than that in preserved GLS (<-15%) patients (-15±4, -19±6, p=0.0001). And, ventricular-arterial coupling was significantly greater in impaired GLS (>-15%) than that in preserved GLS (<-15%) patients (0.73±0.20, 0.63±0.19, p=0.0196). Furthermore, VA coupling was significantly correlated with GLS (R=0.29; p=0.0060) and GCS (R=0.46; p<0.0001).
Conclusion: Global longitudinal strain and global circumferential strain may reflect abnormal VA coupling in clinical settings of HFpEF.

NOVEL ASPECTS OF ENDOTHELIAL CELL FUNCTION

5924 | BENCH
rAAV mediated Thymosin beta4 overexpression induces therapeutic neovascularisation in a porcine model of chronic myocardial ischemia

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Induction of neovascularization using vascular growth factors has emerged as a promising novel approach for promoting cardiac repair and regeneration. Thymosin ß4 (Tß4), a small 4.9 kDa peptide influences cell motility, migration and differentiation. We investigated the role of long-term Tß4 overexpression using recombinant adeno-associated vector Tß4 (rAAV Tß4) in a pig model of normo- and hypercholesterinemic diet in chronic myocardial ischemia.
Methods: Chronic ischemia was induced via reduction stent graft in the circumflex artery, leading to a total occlusion on day 28 (d28). Regional application of saline or rAAV Tß4 (5x10E12 viral particles, d28) was compared with Tß4 transgenic pigs. Global myocardial function (EF, LVEDP) was obtained and of blood flow was measured via fluorescent microspheres (FMI). Regional myocardial function and post mortem angiography (collateral growth) were obtained on day 56. Histological analysis of capillary density (capillaries/field (C/F)) was performed. Hypercholesterinemia was induced via high-fat diet (d0-56).
Results: Tß4 overexpression via rAAV significantly enhanced capillaries (142±4 vs. 67±3 C/F) and collaterals (9±1 vs. 3±1) in the ischemic area. Blood flow was significantly increased in ischemic area (d56, 91±2% vs. 78±3% non-ischemic area). Furthermore, global (EF: 47±4 vs. 29±3%; LVEDP: 12±2 vs. 19±2 mmHg) and regional myocardial function (SES at 150 beats/min: 73±5 vs. 10±6% of non-ischemic area) were increased. Similar results were obtained in transgenic pigs with ubiquitous Tß4 overexpression (EF: 45±2%; LVEDP: 13±1 mmHg SES at 150 beats/min: 76±3% of non-ischemic area). In the pig model of hypercholesterinemia, serum triglyceride level increased from 22±3 to 72±4 mg/dl. Increased neovascularization and heart function could be achieved after rAAV Tß4 application, albeit at a lower level (capillaries: 88±3 vs. 62±2 C/F; collaterals: 6±1 vs. 3±1; EF: 42±4 vs. 28±3%; LVEDP: 14±1 vs. 18±2 mmHg). Long term Thymosin ß4 expression induced neovascularization and improved myocardial perfusion and function. This effect was mimicked in a model of hypercholesterinemia, suggesting an attractive therapeutic potential of using rAAV Tß4 for otherwise no-option patients with ischemic heart disease.

5925 | BENCH
Barley-derived (1.3) beta-D-glucans promotes angiogenesis involving histone H4 acetylation in human endothelial cells and zebrafish under oxidative microenvironment

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Background: Angiogenic response of adult endothelial cells can significantly improve the repair potential of ischemic myocardium; however, it is challenging to

promote it in the presence of oxidative stress. We recently demonstrated that increased global histone H4 acetylation promotes angiogenesis under oxidative microenvironment; thus, the identification of novel natural angiomodulators is a desirable achievement. Barley-derived (1.3)beta-D-glucan (β-D-glucan) is a water-soluble chain of D-glucose polysaccharide with antioxidant properties, but its angiogenic effect is still unknown. We investigated whether the conditioning of adult endothelial cells with β-D-glucan enhances the angiogenic response to oxidative stress involving histone H4 acetylation.
Methods: In vitro, human umbilical vein endothelial cells (HUVECs) chronically exposed to H2O2 (50uM for 24h) were cultured with or without 3% w/v β-D-glucan, then tested for cell viability and tube formation. p-eNOS/eNOS ratio, pAkt/Akt ratio, HIF1-alpha and MnSOD expression, and the level of histone H4 acetylation were evaluated. In vivo, Tg(kdrl:EGFP)s843Tg transgenic zebrafish embryos were treated for 24h with 3% w/v β-D-glucan under oxidative microenvironment prior angiogenesis assay.
Results: HUVECs treatment with β-D-glucan prevented cell death by 87.41±14% ($P \leq 0.004$) and significantly increased tube formation activity by 11±4% under oxidative microenvironment. At the cellular level such effects seem to be mediated by an epigenetic induction of MnSOD expression through significant increase of histone H4 acetylation (+410±34.3%). Finally, similar dose of β-D-glucan was confirmed to prevent vascular depletion in zebrafish embryos chronically exposed to oxidative microenvironment.
Conclusions: Our study revealed, for the first time, that barley-derived β-D-glucan promotes adult angiogenesis under oxidative microenvironment through increased histone H4 acetylation. These findings uncover a novel and unexpected role for dietary β-D-glucan as a critical epigenetic activator of antioxidant activity governing adult angiogenic response.

5926 | BENCH
Downregulation of von willebrand factor prevents angii-induced endothelin-1 expression independently of enos activation in porcine endothelial cells

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Purpose: Angiotensin II (AngII) generated under conditions of myocardial ischemia and reperfusion increases endothelial levels of endothelin (ET)-1, von Willebrand factor (vWF) and anion superoxide (O2-), which lead to progressive coronary endothelial dysfunction. Recent study described that vWF blockade improves endothelial function in coronary patients, but the mechanisms are still unknown. Our study investigated whether the downregulation of vWF modulates the ET-1 level, eNOS activity and O2- generation in porcine aortic endothelial cells (PAOECs) chronically exposed to AngII.
Methods: The silencing of vWF in PAOECs was induced with selective short interference RNA. Protein expression of endothelial vWF, ET-1, eNOS and phospho-Ser1177eNOS (p-eNOS) was measured by western blotting in wild type and vWF-knockdown cells exposed to vehicle or AngII (100nM for 24h). O2- formation was measured by dihydroethidium staining. In additional experiments, wild type and vWF-knockdown cells were treated with phorbol 12-myristate 13-acetate (PMA, 5nM for 48h), a nonsubtype selective agonist of protein kinase type C and inhibitor of eNOS activity.
Results: Nearly 65% silencing of vWF cell viability and growth were not impaired. Levels of ET-1, phospho-Ser1177eNOS (peNOS)/eNOS ratio and O2- were unchanged in vWF-knockdown compared to wild type cells under normal conditions. Conversely, ET-1expression was reduced by 93.7±4% ($P<0.0001$) in the presence of normal p-eNOS/eNOS ratio in vWF-knockdown cells under oxidative microenvironment; although, the intracellular load of O2- was reduced by 33.3±2% in vWF-knockdown cells with lower level of Mn superoxide dismutase. In additional experiments, the inhibition of eNOS activity by PMA did not reverse the downregulation of ET-1.
Conclusions: We demonstrated that vWF-knockdown modulates the response of PAOECs to chronic exposure to AngII by preventing cell death, reducing ET-1 and O2- production without affecting endothelial function. Our findings support the usefulness of vWF as upstream modulator of ET-1 expression under oxidative stress.

5927 | BENCH
Vascular resident endothelial progenitor cells facilitate collateral growth under control of a proteasomal regulator

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Increasing evidences indicate that vascular resident endothelial progenitor cells (VR-EPCs) are present in vessel walls and play an important role in postnatal neovascularization. We previously demonstrated that a particular clonal subset of late outgrowth cells isolated from rat cardiac microvascular cells express several major stem/progenitor cell as well as differentiation markers and form capillary-like structures under endothelial differentiation conditions. We here demonstrate that these VR-EPCs are stained by an antibody that was generated against growing collateral arteries (mAb CTA157-2). This antibody that particularly stained endothelial structures of proliferating collateral vessels bound to cell membranes of these late outgrowing VR-EPCs and inhibited their proliferation via proteasomal activation. Injection of VR-EPCs into the ischemic hindlimb of rats enhanced collateral growth (No. of collateral vessels (micro CT): 4.5±1.0 (Control) vs. 8.1±1.1 (VR-EPCs); $p<0.05$), collateral proliferation (BrdU incorporation: 0.52±0.06 vs. 0.75±0.10; $p<0.05$) and calf muscle blood flow (microspheres ratio for gastrocnemius: 0.19±0.03 vs. 0.40±0.08; $p<0.001$; soleus ratio: 0.11±0.01 vs. 0.19±0.04; $p<0.001$). These effects were inhibited by treatment with mAb CTA157-2 (No of collateral vessels: 5.3±0.4 (Control) vs. 4.3±0.7 (CTA157-2); $p<0.05$ and BrdU incorporation: 0.54±0.17 (Control) vs. 0.40±0.14 (CTA157-2); $p<0.05$). These results indicate that exogenous administration or endogenous mobilization of highly clonogenic VR-EPCs facilitate collateral growth and suggest that VR-EPCs are under particular control of external proteasomal regulators in keeping with their rapid adaptive potential

5928 | BENCH
Induction of superoxide dismutase-2 (MnSOD) by apoptosis signal regulating kinase-1 (ASK1) via activation of NFkB in endothelial cells

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Purpose: Endothelial cell apoptosis precedes myocardial apoptosis in ischemic myocardium, as well as during the reperfusion of ischemic myocardium. Although it remains unclear as to how the endothelial cells undergo apoptotic death during myocardial ischemia-reperfusion, activation of apoptotic signaling could be a major contributor to endothelial apoptosis. ASK1 is a MAP3K that activates apoptotic cascade via activation of JNK. Mitochondrial superoxide dismutase-2 (MnSOD) is an antioxidant enzyme that protects the heart form reperfusion injury. For example, MnSOD is elevated in hearts within 24 hours after ischemic preconditioning and is crucial in the acquisition of tolerance to ischemia. TNFa, which induces MnSOD could protect rabbit hearts from reperfusion injury. Although TNFa induces MnSOD, it also activates ASK1. We hypothesize that ASK1 signaling is a major contributor to endothelial cell death in the ischemic myocardium.
Methods: Human microvascular endothelial cells (HMVEC) were cultured in EGM-2MV with supplements. pcDNA3-ASK1, pcDNA-3ΔASK1 (constitutively active form), and dnASK1 (dominant-negative ASK1) were transfected into HMVEC using Fugene-6 transfection reagent (Roche). In addition, cells were co-transfected with pcDNA3-ASK1 and pcDNA3-JNK-APF, pcDNA3-MKK4 or pcDNA3-MKK7 to determine the transmission of apoptotic signaling mechanism. We also determined the activation of NFkB due to ASK1 expression using electrophoretic mobility shift assay (EMSA).
Results: To our surprise, transfection of ASK1 induced the MnSOD gene expression in endothelial cells, but transfection of dnASK1 did not induce MnSOD. In addition, transfection of pcDNA-3ΔASK1 also induced MnSOD gene expression and expression of MnSOD protein. In contrast, in the presence of JNK inhibitor SP600125 or co-transfection of dominant-negative JNK expression construct resulted in potentiation of MnSOD expression. We also observed that transfection of ASK1 into the HMVEC induced NFkB activation and pSEMutIkB, a superrepressor of NFkB was able to abrogate NFkB activation by ASK1.
Conclusion: We concluded that apoptotic signaling by ASK1 induces antiapoptotic genes such MnSOD and activates NFkB. ASK1 induces both survival and apoptotic signaling, the balance of which may determine whether the endothelial cells would undergo apoptosis or survive. Suppression of JNK favors ASK-1-NFkB signaling resulting in survival of endothelial cells
Funding: The study is supported by NIH grants HL109337 and HL107588 to KCD.

5929 | BENCH
Loss of Sirt3 induces endothelial dysfunction in a ROS-dependent manner and inactivates endothelial SOD2

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Purpose: Sirtuin 3 (Sirt3) is an NAD+-dependent mitochondrial deacetylase that has been shown to protect from oxidative stress by activating Superoxide Dismutase 2 (SOD2), a key scavenger of superoxide. We have reported accelerate # weight gain and impaired metabolic flexibility in atherosclerotic Sirt3 knockout mice. Oxidative stress is a hallmark of endothelial dysfunction. Yet, the role of Sirt3 in this context is unknown. Therefore, we investigated the effect of Sirt3 on endothelial function and oxidative stress using a loss-of-function approach in a mouse model and human aortic endothelial cells (HAEC), respectively.
Methods: 8-week-old male Sirt3 knockout and wildtype mice were fed a high-cholesterol diet for 12 weeks to induce endothelial dysfunction. Aortic rings were explanted and relaxation was assessed in response to increasing doses of acetylcholine in the presence or absence of pegylated superoxide dismutase (PEG-

SOD) or apocynin using isometric force transducers in organ chamber baths. Transient knockdown of Sirt3 in HAEC was induced using siRNA. Superoxide generation was studied using electron spin resonance spectroscopy. Expression analyses were performed by qPCR and western blot.
Results: Endothelial-specific relaxation in Sirt3 knockout mice was impaired compared with controls. Relaxation capacity was restored when superoxide was either scavenged by an excess of PEG-SOD or when its generation was blunted in the presence of apocynin. Transient knockdown of Sirt3 in HAEC increased superoxide generation and decreased SOD2 activity compared with controls. Unexpectedly, SOD2 expression was increased after knockdown of Sirt3. This effect was lost after simultaneous knockdown of the deacetylation-dependent transcription factor CEBP-ß and Sirt3, suggesting a CEBP-ß-dependent transcriptional feedback regulation of SOD2.
Conclusion: Our data indicate that endogenous Sirt3 protects from oxidative stress-induced endothelial dysfunction by activating SOD2. A CEPB-ß-dependent transcriptional feedback regulation of SOD2 is insufficient to compensate for the Sirt3-dependent loss of SOD2 activity. Thus, Sirt3 plays not only a role in a metabolic context by decreasing weight gain and maintaining expedient metabolic adaptation, Sirt3 also contributes to vascular protection.

5930 | BENCH
Increased endothelial insulin signaling leads to endothelial dysfunction via NADPH oxidase activation

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Introduction: Type 2 diabetes poses a major challenge in healthcare management. Insulin resistance is well-documented to affect the production of the anti-atherosclerotic molecule, nitric oxide (NO). The effects of increasing insulin signalling in the endothelium was assessed, using a novel transgenic mouse, over-expressing Type A human Insulin Receptor (HIRECO) in the endothelium.
Methods: Western blotting and RT-PCR were carried out on tissues and isolated endothelial cells from lungs to confirm the presence of human insulin receptor protein levels and mRNA expressions, respectively. NADPH-dependent lucigenin-enhanced chemiluminescence assay was chosen to measure superoxide anion levels. Isolated thoracic aortic rings suspended in organ baths were used to determine vasomotor function. eNOS activity was examined by citrulline assay with 14C-labelled L-arginine. HIRECO were compared to wild type littermates (WT).
Results: Over-expressing human insulin receptors in the endothelium has no effect on development, metabolic phenotypes or blood pressure in HIRECO. Plasma insulin levels were similar following an overnight fast, but were decreased in the HIRECO after glucose challenge. HIRECO mice demonstrated significant endothelial dysfunction measured by a blunted endothelium-dependent vasorelaxation to acetylcholine. Basal NO release was decreased in HIRECO. Endothelium-independent response to sodium nitroprusside remained unchanged. The impaired aortic response to acetylcholine was normalized by the specific NADPH oxidase inhibitor gp91ds-tat, as well as the superoxide dismutase mimetic, MnTmPyP. HIRECO demonstrated significant increase in superoxide anion production compared to WT. This data was supported by a concomitant increase in NADPH oxidase isoform, NOX2 protein expression. Both basal eNOS and Akt phosphorylation levels in isolated endothelial cells of HIRECO mice were enhanced compared to WT. Insulin-stimulated eNOS phosphorylation was decreased in HIRECO whereas Akt phosphorylation remained unchanged. eNOS tyrosine phosphorylation mediated by over-expression of proline-rich tyrosine kinase, PYK2 was significant enhanced in the endothelial cells isolated from HIRECO mice.
Conclusions: These data demonstrate a state of enhanced oxidative stress in a novel murine model of increased insulin sensitivity in the endothelium, leading to reduced bioavailability of NO and endothelial functions. These data also demonstrate for the first time, that increased insulin signaling in the endothelium, increases the generation of superoxide anion via activation of NADPH oxidase and reduces NO bioavailability.

5931 | BENCH
Notch signaling regulates the lifespan of vascular endothelial cells via a p16-dependent pathway

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Purpose: Accumulation of senescent vascular cells occurs in aged vessels, leading to an increase of inflammation combined with a decline of regenerative potential that promote vascular dysfunction and atherosclerosis. Evolutionarily conserved Notch signaling controls cell fate determination and differentiation during development, and is also essential for neovascularization in adults. Although recent studies suggest that the Notch pathway is associated with age-related conditions, it remains unclear whether Notch signaling is involved in vascular aging. The objective of this study was to elucidate the role of Notch signaling in endothelial cell senescence.
Methods and results: Inhibition of Notch signaling, by using Notch1 short hairpin RNA, in human umbilical vein endothelial cells (HUVEC) reduced the maximum population doublings, increased the activity of senescence-associated beta-galactosidase, and up-regulated the expression of aging-associated molecules such as p53, p21, and p16. Likewise, knockdown of the Notch ligand Jagged1 attenuated Notch activity in the neighboring cells, thereby inducing premature senescence. Conversely, over-expression of Notch1 or Jagged1 prolonged the replicative lifespan of endothelial cells. Disruption of p16 restored premature senescence induced by Notch1 deletion. Notch1 positively regulated the expression of inhibitor of DNA binding 1 (Id1) and MAP kinase phosphatase 1 (MKP1), while MKP1 further up-regulated Id1 expression by inhibiting p38MAPK-induced protein degradation. Over-expression of Id1 down-regulated p16 expression, thereby inhibiting premature senescence of Notch1-deleted endothelial cells.
Conclusions: These findings indicate that Notch1 signaling has a role in the regulation of endothelial cell senescence via a p16-dependent pathway and suggest that activation of Notch1 could be a new therapeutic target for treating age-associated vascular diseases.

PREDICTORS OF OUTCOME IN CORONARY ARTERY BYPASS GRAFTING

5939 | BEDSIDE
Angiographic factors predict long-term venous and arterial graft patency

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Purpose: Long-term venous and arterial coronary artery bypass graft (CABG) patency is influenced by many factors. Most of them are still poorly understood and matter of debate. In this study we aimed at evaluating the value of angiographic factors in predicting failure of both venous and arterial graft.
Methods: We retrieved from our angiographic database 148 patients who underwent venous and/or arterial CABG and for whom a control coronary angiography at more than one month after surgery was available. Clinical and laboratory data were collected for all patients. Pre-CABG and follow-up angiographies were analyzed in order to evaluate diameter stenosis (DS, %), stenosis length (mm), Sullivan Score and Jeopardy Duke score. Patients with venous or arterial patent graft were used respectively as control for venous or arterial graft failure, irrespective of the patency status of a possible coexisting arterial graft for the former and of a possible coexisting venous graft for the latter. In patients with either venous or arterial graft failure all angiographic parameters referred exclusively to the occluded graft-treated vessel while in patients without either venous or arterial graft failure all angiographic parameters represented mean of those observed on all graft-treated vessels.
Results: Within the overall population, 39 patients (26%) experienced graft failure at follow-up (mean follow-up 11.3±4.6 months). Patients with venous graft failure [26 (20%)] had significantly lower DS [84% (±6) vs 88% (±7), p=0.013), shorter stenosis length [7.7 (4.6-11.4) vs 11.3 (9.3-11.6), p=0.01] and lower Sullivan Score [3.7 (1.9-5.4) vs 4.7 (3.3-7.4, p=0.013] as compared with those without venous graft failure. Patients with arterial graft failure [13 (11%)] had significantly lower DS [82% (±6) vs 87% (±6), p=0.008), shorter stenosis length [6.7 (4.7-9.6) vs 11.3 (8.5-11.6), p=0.001] and lower Sullivan Score [2.7 (2.0-4.4) vs 4.7 (3.0-7.0, p=0.023] as compared with those without arterial graft failure. No differences were observed in clinical, laboratory data and Jeopardy Duke score for both venous or arterial graft failure.
Conclusions: Venous and arterial graft failure are associated with less severe/shorter stenosis and less extensive atherosclerosis of the grafted vessel thus suggesting that both stenosis features and disease extent should be assessed prior to surgical myocardial revascularization.

5940 | BEDSIDE
Predictors of and clinical outcomes after internal mammary artery graft failure: insights from the PREVENT-IV trial

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Background: The internal mammary artery (IMA) is considered the gold standard for bypassing the left anterior descending (LAD) coronary artery in patients undergoing coronary bypass surgery (CABG). Systematic evaluation of predictors for and long-term outcomes following IMA failure is lacking.
Methods: Participants in the PREVENT-IV trial who underwent IMA-LAD revascularization and 12-18 month angiographic follow-up were included (n=1,538). Logistic regression with stepwise variable selection was used to identify characteristics associated with IMA graft failure (≥75% stenosis). The relationship between IMA failure and long-term outcomes (all-cause mortality, myocardial infarc-

tion, or repeat revascularization), was assessed using Cox proportional hazards modeling and adjusted for potential confounders.
Results: IMA graft failure occurred in 132 (8.6%) subjects. Patients with IMA failure had less diabetes, a lower grade LAD stenosis, and worse graft quality. After adjustment, predictors for IMA failure were diabetes (odds ratio (OR): 0.55, 95% confidence interval (CI): 0.36-0.83), p=0.004), and LAD stenosis <75% (OR: 1.76, 95% CI: 1.20-2.60), p=0.004). LAD stenosis, but not diabetes remained predictive in an alternative model in which IMA failure was defined as a composite of either ≥75% stenosis or death before angiography. The model for clinical outcomes found that IMA failure was associated with a significantly higher incidence of subsequent acute (≤14 days of angiography) events and a trend towards more subsequent remote events (see Fig. 1).

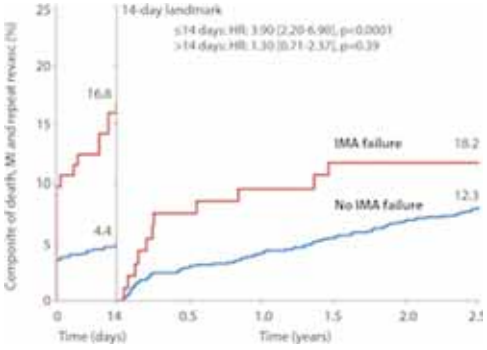

Figure 1

Conclusion: Patients with less severe pre-operative LAD stenosis are at higher risk for IMA graft failure. While the long-term clinical implications are less clear, IMA graft failure is associated with increased early adverse clinical events.

5941 | BEDSIDE
Can serial cardiac troponin I measurements following coronary artery bypass grafting be used to identify early graft occlusion?

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Purpose: The aim of this study was to determine if serial measurements of cardiac troponin I (cTnI) following coronary artery bypass grafting (CABG) can be used to identify early graft occlusion.
Methods: From September 2011 to June 2012 patients with stable angina pectoris and 2-3-vessel disease, undergoing elective on-pump CABG were considered. Blood samples for cTnI measurements were taken 9 times pre- and postoperatively. Thus, time zero was defined as the time of aortic cross clamp removal, and subsequent samples were drawn 2, 4, 6, 12, 24, 48 and 72 hours later. cTnI concentrations were analysed on the Abbott Architect c16000 system, which operates with an upper reference limit of 30 ng/L. A cardiac CT angiography (CCTA) was scheduled within 14 days following CABG. Graft occlusion was defined as the presence of a 100% graft stenosis or in case the graft was not visible on the CCTA.
Results: A total of 34 patients had a CCTA performed. The time from CABG to CCTA was a mean of 6.5 days (± 2.9). The mean age of the patients was 65.9 years (±8.3) with a majority of men, 85% (29/34). A total of 104 distal anastomoses were performed in the 34 patients. CCTA demonstrated a total of 12 occluded grafts (11.5%) in 8 patients. Three patients had a myocardial infarction (MI) in the time period from CABG to CCTA. Two of the MIs occurred <72 hours following CABG. Only in one MI patient an occluded graft was found. The peak cTnI value did not differ significantly between the 8 patients with one or more occluded grafts (10850 ng/L) and the 26 patients without graft occlusion (10950 ng/L) (p=0.935)

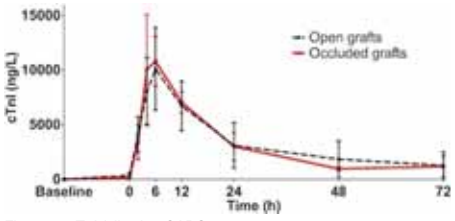

Figure 1. cTnI following CABG.

Conclusion: In patients with stable angina pectoris undergoing elective CABG, serial postoperative measurements of cTnI were not useful in identifying patients with early graft occlusion.

5942 | BEDSIDE
Mortality impact of previous coronary angioplasty in the long-term follow-up of patients with acute coronary syndromes submitted to coronary artery bypass surgery during the same hospitalization

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Purpose: There is strong evidence in the literature suggesting that previous percutaneous intervention (PCI) has a negative impact in the outcome of patients (pts) submitted to coronary artery bypass graft surgery (CABG). However, the evidence regarding pts with ACS and/or long-term outcome data for this population, the purpose of this study, is very scarce.
Methods: We analyzed retrospectively a non-selected population of 461 pts (mean age 64.5 years, 70.9% men) with ACS submitted to CABG during the same hospitalization, out from 4100 ACS pts included prospectively in a dedicated databank. The mean (±SE) follow-up (FU) time was 4.56±0.18 years (maximum 13.9 years). The Pearson Chi-square and the Tarone-Ware tests were applied as indicated. Adjusted models utilizing the Cox stepwise regression method were developed in order to adjust for confounder baseline and in-hospital factors.
Results: During the in-hospital phase the Odds-Ratio (OR) for mortality according to presence/absence of previous PCI was 1.3 (P=0.45). During FU, the Kaplan-Meier survival time (mean ± SE) for the groups with presence or absence of previous PCI were, respectively, 8.43±0.68 years and 9.70±0.34 years (P=0.085). Excluding pts with interventricular septum defect (IVSD) and cardiac tamponade - CT (N=14), the figures for pts with or without previous PCI were, respectively: for in-hospital mortality OR=1,38, P=0.37; mean survival times 8.50±0.68 years and 9.90±0.34 years (P=0.047). In the adjusted models, for the whole population the following variables correlated significantly and independently with mortality: age (P<0.001, HR per year=1.049), in-hospital cardiogenic shock (P<0.001, HR=3.54), IVSD (P=0.001, HR=4.55), previous PCI (P=0.018, HR=1.63), previous stroke (P=0.006, HR=2.83), CT (P=0.031, HR=3.12), and ST-elevation-MI (P=0.046, HR=0.67). Excluding IVSD and CT, the results were: age (P<0.001, HR per year=1.049), in-hospital cardiogenic shock (P<0.001, HR=3.28), previous stroke (P=0.008, HR=2.86), previous PCI (P=0.027, HR=1.59) and ST-elevation-MI (P=0.041, HR=0.65).
Conclusion: The presence of previous PCI correlates with worse prognosis in patients with acute coronary syndromes submitted to surgical coronary revascularization during the same hospitalization.

5943 | BEDSIDE
Comparison of euroscore i, ii and acef for risk prediction after on-pump and off-pump cabg

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Purpose: The role of new scores in risk prediction after CABG is not defined. Our aim was to evaluate the predictive properties of ES II and ACEF, as compared to ES I, after off-pump and on-pump CABG.
Methods: All patients submitted to isolated CABG between Jan2010 and Dec2013 were included. Demographic, clinical data, operative variables, both ES I and ES II, and ACEF were evaluated, and outcomes included in-hospital/30 days mortality and MACCE. Predictive ability of ES II and ACEF was evaluated for performance (observed/expected mortality, O/E), calibration (Hosmer-Lemeshow), discrimination (ROC curve) and Net Reclassification Improvement (NRI).
Results: We included 1220 pts (age 63±10a, 68,3% male). Off pump in 54,5% of pts. Mean ES I, ES II and ACEF predicted risk were 3,75%, 1,63% and 2,41%. Global all-cause mortality was 3,0%. Off-pump had lower mortality (1,7% vs 4,7%, p=0,002), lower PO bleeding (1,0% x 3,0%, p=0,035) and stroke rate (3,9% vs 6,7%, p=0,015), but more new revascularization (1,5% x 0,2%%, p=0,006). Multivariable analysis showed that On Pump (OR=3,08, IC95 1,22-7,80, p=0,017) and EuroSCORE II (OR=1,29, IC95 1,04-1,60, p=0,023) were independent predictors of in-hospital/30 days mortality. Performance of ES I, ES II and ACEF in the 4 risk strata was measured by O/E ratio (ES I: 1,19, 0,60, 0,99 e 0,1; ES II: 0,85, 2,54, 2,06 and 1,50; ACEF: 2,26, 0,67, 0,91 and 1,26). ES II was best in low and very high risk, and ACEF was adequate in high and very high risk groups. ES I was adequate only in low risk. The best performance was ES II in Off-pump group (O/E 1,11, 95 IC 1,03-1,22). Callibration in the entire cohort was poor for ES I and adequate for ES II and ACEF (Hosmer-Lemeshow p=0,020, 0,158 and 0,567, respectively). In Off-pump ES 2 and ACEF also were well calibrated (p=0,251 and 0,681). Accuracy of ES II was higher than ES I and ACEF in entire cohort, off-pump and on-pump groups (C stat= 0,711, 0,652 and 0,724 (ES II); 0,650, 0,518 and 0,699 (ES I); 0,663, 0,575 and 0,689 (ACEF) respectively; DeLong test p<0,05 for the 3 comparisons). ES II greatly improved risk classification compared to ES I (NRI total: +35%, NRI events: +83%, NRI nonevents: -48%). In Off-pump, reclassification was even better (NRI total: +48%, NRI events: +90%, NRI nonevents: -42%).
Conclusions: ES II and ACEF had moderately fair clinical performance. ES II was the only independent predictor of death, showed the best accuracy compared to ES I and ACEF, and improved risk reclassification in many patients. ES II is the best risk score for risk prediction after CABG.

5944 | BEDSIDE
Is pulmonary function assessment before coronary artery bypass graft surgery always necessary?

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Purpose: Postoperative pulmonary complications (PPC) contribute significantly to overall morbidity and mortality of coronary artery bypass graft surgery (CABG). As an attempt to prevent PPC, pulmonary function tests (PFTs) are routinely used as a standard-of-care for preoperative risk assessment. We aimed to determine whether preoperative PFTs are predictive of PPC.
Methods: This retrospective study was conducted in consecutive patients who underwent non-urgent CABG, between 2003 and 2008, in our tertiary care institution. Pulmonary function was evaluated through clinical and functional assessment. PPC was defined as any clinically significant pulmonary abnormality (disease or dysfunction) that adversely affected the clinical course.
Results: Of the 203 patients included in the study, 50 (24.6%) had a pathological pattern: 18 (8.9%) had PFTs consistent with at least class II chronic obstructive pulmonary disease and 1 (0.5%) had a pure restrictive pattern. We identified 14 (6.9%) postoperative PPC. Patients with preoperative abnormal clinical exam and/or chest x-ray did not present significantly more PPC (4/42 [9.5%] vs 10/161 [6.2%], p=0.49). The incidence of PPC in patients with abnormal preoperative PFTs did not significantly differ from that of patients with normal or sub-normal ones (2/19 [10.5%] vs 12/184 [6.5%], p=0.63). We found no significant difference when we compared the group presenting abnormal clinical exam/chest x-ray and PFTs, and the group with normal clinical exam/chest x-ray and PFTs (2/14 [14.3%] vs 10/156 [6.4%], p=0.26).
Conclusions: PFTs were not useful to predict the incidence of postoperative PPC. Therefore, it does not seem to be relevant to perform these tests systematically before CABG.

5945 | BEDSIDE
The transfusions conundrum in cardiac surgery: does age matter?

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Purpose: Red blood cells (RBCs) transfusion is a well-known predictor of acute kidney injury (AKI) and death after cardiac surgery procedures. This study explored whether a similar effect existed among octogenarians.
Methods: Study population included 1765 consecutive adult patients undergoing cardiac operations on cardiopulmonary bypass from 2011 to 2013 in a single centre (age: 67.6±10.3; female: 33.1%; redo: 6.2%; urgent/emergent: 12.9%; isolated CABG: 40.1%; isolated valve procedures: 30.4%; combined: 26.7%). The relationship between RBCs with both survival and AKI, and any interaction by age (<80 years versus ≥80 years) was estimated. A propensity score for the likelihood to receive red blood cell transfusion was calculated with multivariable logistic regression to balance the effect of confounding factors. Logistical estimation curve was developed to seek for the interaction between this propensity score and age. Age and propensity score for transfusions were then forced into multivariable logistic models for study outcomes.
Results: Patients receiving RBCs (41%) had more comorbidities irrespective of age. Patients 80 years of age or older underwent transfusion more often than patients younger than 80 years (52.8% versus 39.7%; p<0.001). Mean propensity score in octogenarians was 0.53±0.3 vs 0.39±0.3 in younger patients (p<0.0001) with a twofold increase in the relative risk for transfusion. Anyhow, age did not independently predicted the need for RBCs. AKI and fatality rates were significantly higher in transfused subset irrespective of age. Nevertheless older age per se did not prove an independent predictor of AKI and fatality.
Conclusions: Octogenarians receive RBCs more often than do younger patients. Frailty and not age per se confers an increased risk of RBC transfusion and worse outcomes. Careful evaluation of preoperative patient profile is mandatory in octogenarians referred for cardiac surgery.

5946 | SPOTLIGHT
Assessment of performance and communication of results to add quality in heart surgery

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Introduction: One of the main challenges of current hospital management is to assess the medical team. The medical team performance assessment model should favor evidence-based comparisons
Method: In 2011, a performance assessment related with the medical team performance at work was designed to comply with medical ethical standards and to follow internal guidelines. A meeting was held to disseminate the assessment model among the heart surgery teams, in which we had 100% compliance and agreement from physicians. The assessment was divided into three categories of indicators: outcomes, processes and compliance with institutional protocols, goals based on international indicators and each indicator was scored (10 to 50).
Results: As shown in the table below.

Assessed item		2011	2012	2013	
Death	50	0	0	50	Below STS expectation
Readmission	30	0	0	30	Goal ≤10%
Discharge within 5 days	30	30	30	30	Goal above STS expectation + 20% or >50%
LOS > 14 days	30	30	30	30	Goal below STS mean expected score
Mediastinites	30	0	0	30	Goal below STS mean expected score
Stroke	30	30	0	0	Goal below STS mean expected score
Reoperation	30	30	30	30	Goal below STS mean expected score
More than 4 units of CH	10	10	10	10	Goal below 15%
Blood transfusion	30	0	0	30	Goal below 40%
Operative wound infection rate	50	0	0	50	Goal below 10%
STS form	30	30	30	30	Goal above 80%
Urinary tract infection	15	15	15	15	≤ UTI density at the hospital
Bloodstream infection	15	15	15	15	≤ BSI density at the hospital
Informed term and surgical planning	5	5	5	5	Completed before admission
Completed patient record	5	5	5	5	All completed
Client perception	50	50	50	50	Opinion survey and 30 days after
Total	440	250 (57%)	220 (50%)	410 (93%)	

Conclusions: The assessment of the performance of heart surgical teams is a tool used to improve outcomes and clinical care, has a positive impact as it enables the creation of improvement strategies that engage the surgical teams and the organization's managers.

5947 | BEDSIDE
Mortality reduction with IABP prior to emergency CABG in patients with cardiogenic shock

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Objectives: Patients with cardiogenic shock undergoing coronary artery bypass graft (CABG) surgery have been supported by intraaortic balloon counter pulsation (IABP) therapy, according to the recommendations. Recently, the benefit of IABP support has been doubted, and the optimal starting point for IABP therapy, i.e. before or after surgical revascularization, remains questionable.
Methods: In a single-center retrospective study consecutive patients with cardiogenic shock undergoing emergency CABG in 2008, 2009 and 2010 were supported by IABP therapy either beginning before ("IABP-before" group) or after ("IABP-after" group) revascularization, with 150 patients in each group. In the IABP-before group, IABP support was started either prior to or at the beginning of the CABG operation, in the IABP-after group at the end of the CABG operation. All patients (average age 68 years; 32% women) received the best available therapy with the aim of early CABG. After CABG, the duration of IABP support in the IABP-before group was 4.2±1.9 and in the IABP-after group 5.8±4.1 days.
Results: At 30 days post CABG operation (POD 30), all-cause mortality was slightly lower in the IABP-after group, albeit without significance, than in the IABP-before group (33% vs. 37%, respectively). Conversely, after 1 year the IABP-before group showed a significantly lower all-cause mortality rate than the IABP-after group (41% vs. 52%, respectively; p=0.02). Complications such as major bleeding, peripheral or intestinal ischemia, sepsis and stroke did not differ significantly between the two groups.
Conclusion: IABP support initiated before surgical revascularization markedly reduced the 1-year mortality in patients with cardiogenic shock undergoing early CABG revascularization in contrast to IABP therapy beginning after surgical revascularization. These beneficial effects were not obvious at 30 days. Initiation of IABP therapy before CABG did not cause an increase in IABP-related complications. IABP support does benefit patients in cardiogenic shock due to acute onset of ischemic origin with urgent need for coronary revascularization.

IMPROVING DIAGNOSIS OF STABLE CORONARY DISEASE

5948 | BEDSIDE
Endothelial progenitor cell homing in human myocardium in patients with coronary artery disease

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Purpose: Endothelial progenitor cells (EPCs) are mobilized from bone marrow

into peripheral blood, contributing to the revascularization of ischemic areas, to endothelial repair and to the physiological maintenance of vascularization. EPC mobilization and homing has been primarily linked to ischemia and inflammation presence. While the presence of circulating EPCs has been widely evaluated in different diseases, few studies tried to evaluate the presence of EPCs in human vital myocardium. Aim of our study was to investigate EPC levels both in peripheral blood and in myocardium in the same patients at the same time, evaluating the correlation with coronary artery disease (CAD) presence.
Methods: 36 consecutive patients admitted either for valve replacement surgery or ascending aorta substitution (n=14, group A) or for coronary artery bypass grafting surgery (n=22, group B) were enrolled for the study. Group A patients (4 males, 10 females, age 75.1±7.0 years) had non-ischemic heart disease with no evidence of CAD presence, while Group B patients (13 males, 9 females, age 76.2±4.5 years) comprised mono- (9 out of 22), bi- (7 out of 22), or tri- (6 out of 22) diseased coronary vessels (CAD presence, evaluated as a stenosis >75%). EPC (CD34+KDR+) levels were assessed before the intervention by flow cytometry on whole blood (circulating EPCs) and by immunohistochemistry on a right atrial appendage segment collected during cardioplegia induction (tissue EPCs).
Results: In myocardial tissue, EPCs were primarily located inside the endothelium or the interstitium at epicardiac level. A significant increase of tissue EPCs ($p<0.001$), accompanied by a significant reduction of circulating EPCs ($p<0.01$) was observed in group B patients, characterized by CAD presence, as compared to group A patients (tissue EPCs: Group A 0.218±0.052 vs. Group B 0.533±0.211 EPCs/mm^2; circulating EPCs: Group A 87.5±16.6 vs. Group B 57.4±6.9 EPCs/ml).
Conclusion: Our data show an opposite effect of CAD presence on circulating and tissue EPCs. The presence of CAD disease and the consequent chronic ischemia could represent a trigger to increase EPC recruitment through mobilization from bone marrow and homing in myocardium, supporting the hypothesis of EPC involvement in the reparative mechanisms of ischemic myocardium. Further studies in a larger population of patients are required to support our hypothesis as well as to prospectively define the importance of increased levels of EPCs in myocardium.

5949 | BEDSIDE
Proprotein convertase subtilisin/kexin type 9 (PCSK9) concentrations predict event-free survival in patients with stable coronary disease on statins

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Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) increases serum LDL-C concentrations by enhancing degradation of hepatic LDL-receptors. Therefore, PCSK9 inhibitors emerge as a new option to lower LDL and as therapeutic tools in the prevention of cardiovascular (CV) disease. The association of PCSK9 and event-free survival has not been clarified prospectively in high-risk patients. This prospective cohort study analyzes risk prediction with PCSK9 serum concentrations in patients with stable coronary artery disease (CAD) on statin treatment.
Methods and results: Fasting PCSK9 concentrations were measured in 504 consecutive patients with stable CAD confirmed by angiography. The median age was 68 years, 83% of patients were male and 95% were treated with statins. Oral glucose tolerance tests were performed in all patients without known diabetes for metabolic characterization. PCSK9 concentrations correlated strongly with fasting triglycerides ($R=0.33$, $p<0.0001$) and PCSK9 was associated with statin treatment, age, hypertension, hyperlipidemia, C-reactive protein, hemoglobin A1c, fasting insulin and total cholesterol. No association was observed with body mass index, waist circumference, LDL- or HDL-cholesterol (linear regression analyses and Spearman's rank correlation).
The primary outcome was the composite endpoint of cardiovascular death and cardiovascular hospitalization for acute coronary syndrome or hospitalization for unplanned, symptom-induced coronary angiography and revascularization (including bypass surgery) within 48 months follow-up. Comparison of event-free-survival between PCSK9 tertiles showed that serum concentrations of PCSK9 predicted CV outcomes (PCSK9 >622ng/ml vs. <471ng/ml: univariate HR 1.55, 95%-CI 1.11-2.16, p=0.009). In multivariate analyses (Cox proportional hazards regression), PCSK9 remained predictive after adjustment for age, gender, risk factors, medication, glucose metabolism and cholesterol (multivariate HR 1.44, 95%-CI 1.02-2.44, p=0.04). The association of PCSK9 levels with CV events was reduced to non-significance after adjustment for fasting TG.
Conclusion: PCSK9 serum concentrations predict cardiovascular events in patients with stable coronary artery disease on statin treatment. Fasting triglycerides, but not LDL-cholesterol, are correlated with PCSK9 and modify risk prediction by PCSK9.

5950 | BEDSIDE
microRNA expression in circulating microvesicles predicts cardiovascular events in patients with coronary artery disease

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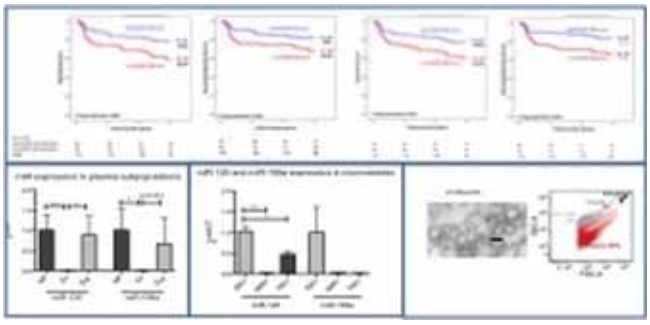
Background: Circulating microRNAs (miRs) are differentially regulated and selectively packaged in microvesicles. We evaluated whether circulating vascular and endothelial miRs in patients with stable coronary artery disease (CAD) have prognostic impact on the occurrence of cardiovascular events.
Methods and results: Ten miRs involved in the regulation of vascular performance including miR-126, miR-222, miR-let 7d, miR-21, miR-20a, miR-27a, miR-92a, miR-17, miR-130 and miR-199a were quantified in plasma and circulating microvesicles (MVs) by RT-PCR in 181 stable CAD patients. The median follow-up time for major adverse cardiovascular event (MACE)-free survival was 6.1 (6.0/6.4) years. Events occurred in 55 (31.3%) patients. There was no significant association between cardiovascular events and plasma level of analysed miRs. In contrast, increased expression of miR-126 and miR-199a in circulating MVs (MmiR) was significantly associated with a lower MACE rate. In multivariate analysis, levels of MmiR-126 above the median were predictors of MACE-free survival (HR: 0.381, 95% CI: 0.190-0.764; P=0.007) and revascularization (HR: 0.391, 95% CI: 0.178-0.861; P=0.02). Likewise, an increased level of MmiR-199a was associated with a reduced risk of MACE (HR: 0.414, P=0.01) and revascularization rate (HR: 0.305, P=0.004) in multivariate analysis. miR expression analysis in plasma compartments revealed that miR-126 and miR-199a are mainly present in circulating microparticles. In vitro, endothelial cells were found to be the major cell source of miR-126- and miR-199a-containing MVs.



Conclusion: Expression of microvesicle-incorporated miR-126 and miR-199a but not freely circulating miRs predicts the occurrence of cardiovascular events in stable CAD patients.

5951 | BEDSIDE
Association between plaque vulnerability and eicosapentaenoic acid to arachidonic acid in non-hypercholesterolemia patients

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Background: Recent reports suggest that eicosapentaenoic acid to arachidonic acid ratio (EPA/AA ratio) is a new risk marker for coronary artery disease. The aim of this study was to evaluate the relationship between EPA/AA ratio and coronary plaque vulnerability in non-hypercolesterolemia patients.
Methods: Consecutive non-hypercolesterolemia patients with stable angina pectoris (n=76) without any lipid lowering therapies were divided into two groups based on the presence of in vivo thin cap fibroatheroma (TCFA) in de novo target vessels assessed by virtual histology intravascular ultrasound (VH-IVUS): VH-TCFA(+) group; n=18 or VH-TCFA(–) group; n=58.
Results: Total cholesterol, low-density lipoprotein cholesterol, high-density cholesterol, and triglyceride levels were similar between the two groups. On the other hand, EPA/AA ration was significantly lower in Patients with in vivo TCFA than patients without in vivo TCFA (0.39±0.18 vs 0.51±0.23, $p<0.05$). In addition, docosahexaenoic acid level was also significantly lower in patients with in vivo TCFA (117.4±29.5 vs 140.4±35.4, $p<0.05$). Percent necrotice core volume was significantly higher in TCFA group (25.3±5.2% vs 19.6±4.3%, $p<0.01$).

Laboratory data

	TCFA(+)	TCFA(–)	p
T-Cho, mg/dl	172.1±26.4	179.6±26.1	0.29
LDL-C, mg/dl	107.1±19.1	108.4±18.7	0.8
HDL-C, mg/dl	42.9±14.5	45.0±11.0	0.52
TG, mg/dl	127.4±66.2	111.2±71.1	0.4
EPA, μg/ml	54.3±37.3	72.6±38.5	0.08
AA, μg/ml	136.6±32.1	142.4±28.0	0.46
DHA, μg/ml	117.4±29.5	140.4±35.4	0.01
EPA/AA	0.39±0.18	0.51±0.23	<0.05

Conclusion: Low EPA/AA ration and low docosahexaenoic acid level might

be associated with coronary plaque vulnerability even in patient with non-hypercolesterolemia.

5952 | SPOTLIGHT
CPET in the diagnosis of CAD – a new approach

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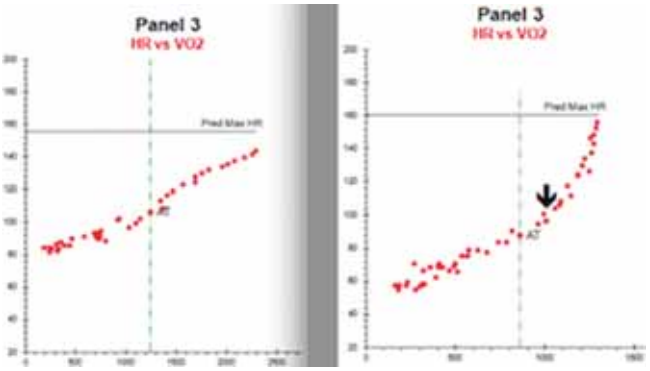
Purpose: Prospective study to examine the diagnostic accuracy of a new exercise-based parameter (abrupt steepening of HR response) in late exercise to diagnose macro-vascular CAD.
Method: 1000 CPX performed in symptomatic patients & 50 Angiograms in a single centre.
Results: Patients without inducible ischemia have a linear HR response as a function of VO2 throughout exercise (Fig. 1). Patients with inducible ischemia develop mechanical dysfunction and a compensatory steepening of HR response (curvilinear) (Fig. 2); this signifies clinically significant global ischemic burden. Fifty consecutive patients with an abnormal response underwent angiography. The sensitivity and specificity for significant large vessel atherosclerosis (one or more vessels with >50% stenosis) was 92% (Table 1).



Figures 1 & 2

Table 1. CPX relationship to coronary angiogram

	Coronary angiogram (Gold Standard)		
	Positive	Negative	
CPX outcome			
Test outcome positive	35 (TP)	1 (FP)	Precision = 97%
Test outcome negative	3 (FN)	11 (TN)	NPV = 78.5%
	Sensitivity = 92%	Specificity = 92%	Accuracy = 92%

NPV, negative predictive value.

Conclusion: In the contracting Ischemic Myocardium, an oxygen supply-demand mismatch results in diastolic dysfunction causing the stroke volume response to deteriorate and HR response to steepen with a progressively increasing work rate past the ischemic threshold. This methodology is seen far more frequently than ST depression and is highly sensitive to the presence of a physiologically significant ischemic burden.

5953 | BEDSIDE
Diagnostic yield of invasive coronary angiography in the workup of patients suspected of coronary artery disease: referral strategies in a tertiary care hospital

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Purpose: Invasive coronary angiography (ICA) is an important exam in the diagnostic workup of patients suspected of stable coronary artery disease (CAD). However, recently published studies describe 30-45% rates of normal coronary arteries. We sought to describe the referral strategy for ICA in a tertiary care hospital in comparison to the 2013 ESC guidelines.
Methods: All elective diagnostic ICAs performed in a tertiary care hospital from 2008 to 2012 to evaluate patients suspected of having CAD were reviewed. Patients with known CAD or unstable presentation were excluded from the analysis. We collected data on patients' clinical status and symptoms and non-invasive diagnostic tests performed before referral for ICA. Pretest probability (PTP) was calculated with the 2011 modified Diamond-Forrest model. The ICA was classified as normal if there was no epicardial coronary stenosis >30%, non-obstructive CAD if the stenosis was ≥30% but <70% (<50% for left main stenosis) and obstructive CAD for left main stenosis ≥50% or other epicardial coronary stenosis ≥70%.The result of the non-invasive diagnostic test performed before ICA was classified as positive, negative or inconclusive. Results are presented as mean±standard deviation or proportion of cases.
Results: From the 13,864 ICAs performed in the 5-year period, we identified a total of 2,818 ICAs fulfilling the inclusion criteria. Sixty-nine percent were male and the mean age was 63.6±9.9 years. Most patients (64.2%) demonstrated typical angina and 7.9% complained of symptoms other than chest pain. One patient had a low PTP of CAD. From the 2,755 (97.7%) patients with intermediate PTP, 468 (17%) didn't performed any prior non-invasive stress test.
Most patients (69.4%) performed one non-invasive test, 13.5% 2 tests and only 0.3% 3 tests before ICA. The most common non-invasive evaluation was performed by treadmill exercise test (63%), followed by SPECT (22.3%), CTA (10.6%), stress echocardiography (1.1%) and stress CMR (only 11 patients). Five percent of the total population was directly referred for ICA after CTA.
A total of 986 ICAs (33.5%) showed normal coronary arteries and 14.3% non-obstructive CAD. On the other hand, an obstructive coronary stenosis was present in 1538 ICAs (52.3%), mostly 1-vessel disease (728 ICAs).
Conclusion: We report a 34% rate of normal ICAs in a tertiary care hospital population investigated for possible CAD. According to the current 2013 ESC guidelines, there is a need for improvement in patient referral for ICA in order to maximize its potential in the diagnosis and treatment of obstructive CAD.

5954 | BEDSIDE
Periprocedural myocardial infarktion - does it really matter?

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Purpose: Cutoff values for troponin to define periprocedural myocardial infarction (type 4a) have been defined by consensus, but the prognostic value of this definition has not been carefully evaluated. The purpose of this study was to determine the incidence of elevated biomarkers after elective PCI using the cut off set by the expert consensus document and ESC clinical practice guideline "The Third Universal Definition of Myocardial Infarction" and to clarify whether this carries independent prognostic significance.
Methods: We performed a historical prospective follow up study of a cohort of patients with stable angina pectoris who underwent elective PCI in a single high volume center from 2000 to 2013. To link and follow the patients we used multiple national Danish registries. We aligned older values of Troponin T concentration (cTnT) to modern high sensitive values in ng/L.
Results: Of the included 2760 patients, 1064 (38.5%) patients had elevated cTnT above 5 x the 99th percentile upper reference limit (URL) after PCI. Follow-up was mean 5.8 years and a total of 15891 years. In stratified analysis of the hazard rates for time until death after peak post-PCI cTnT there was no statistically significant difference regarding all-cause mortality or the combined end-point of death or new onset heart failure. Figure 1 shows Kaplan-Meier plot of peak post-procedural cTnT in five groups. There was also no significant difference in multivariant analysis adjusting for gender and age.

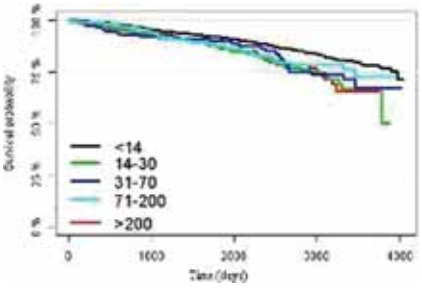

Figure 1

Conclusion: The incidence of elevated biomarkers above the defined 5x URL in our population was high, but this carries no apparent independent prognostic value. Our data suggest that routine measurement of cTnT or CK-MB after elective PCI is not relevant barring procedural complications.

5955 | BEDSIDE
Diagnostic yield of upstream non-invasive testing before coronary angiography for suspected coronary artery disease

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Purpose: The purpose of this study was to assess the diagnostic yield of upstream non-invasive testing before elective invasive coronary angiography (ICA) in patients with suspected coronary artery disease (CAD).
Methods: Cross-sectional observational study of 2327 consecutive patients (61% male, mean age 65±10 years) without known CAD undergoing elective ICA due to chest pain symptoms in two centres between January 2008 and December 2012. The proportion of patients with obstructive CAD (defined as the presence of at least one ≥50% stenosis on ICA) was assessed according to the use of noninvasive testing.

Results: Overall, 1963 of the 2327 patients (84.4%) had a positive noninvasive test: stress myocardial perfusion imaging (41.3%), exercise ECG (35.9%), coronary CT angiography (3.7%), stress echocardiogram (3.3%), or stress cardiac magnetic resonance (0.1%). Referral without previous testing occurred in 15.6% of cases. The prevalence of obstructive CAD was 61.5%. This prevalence was numerically higher in those with previous testing (62.3% vs. 57.4%, respectively), but did not reach statistical significance p=0.089). Among those with upstream testing, obstructive CAD on ICA was more frequent when anatomical rather than functional tests were used (81.4% vs. 61.4%, p<0.001). Conventional risk factors (except for hypercholesterolemia) and anatomical testing were all independent predictors of obstructive CAD, with adjusted odds ratios (95% confidence interval) of 3.62 (3.00-4.36) for male gender, 1.04 (1.03-1.05) for age, 2.09 (1.52-2.87) for current smoking, 1.53 (1.25-1.87) for diabetes, 1.27 (1.00-1.61) for hypertension, and of 2.99 (1.69-5.29) for coronary CT angiography.
Conclusions: Nearly 40% of patients without known CAD undergoing elective ICA did not have obstructive lesions, even though more than 4/5 had a positive noninvasive test. Functional tests were more often used but appear to be outperformed by anatomical testing as gatekeepers for ICA.

5956 | BEDSIDE
Gender differences in the management of stable angina pectoris

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Aims: Several studies have reported gender differences in stable angina pectoris (SAP) treatment. We compared the contemporary use of cardiovascular medication and invasive treatment in men and women with SAP.
Methods: We followed 6,040 patients (27% women) with suspected SAP referred for first-time coronary angiography in Eastern Denmark during 1999–2009 who had obstructive (≥50% stenosis) coronary artery disease (CAD). All patients were free of prior cardiovascular disease. Outcomes were a composite of percutaneous coronary intervention and coronary artery bypass grafting and medical treatment categorized by drug group all within 1 year of angiography and found by registry linkage.
Results: Severity of CAD differed by sex. Women had more single-vessel disease (48% vs 19%), and men had more three vessel disease (68% vs 35%) (P<0.001 for distribution difference). In total, 1,074 women and 3,328 men were revascularized within 1 year of angiography. Women were less likely to be revascularized (66% vs 76% in men, P<0.001; Table) with an odds ratio of 0.76 (95% CI, 0.62–0.92) after multivariable adjustment for age, severity of CAD, abnormal ventricular function and diabetes. Aspirin was more frequently used in women than men (88% vs 85%, P=0.004) while statins and beta-blockers were used equally frequently (91% vs 90%) and (72% vs 74%), respectively.

Table 1. Treatment within 1 year of coronary angiography by sex in patients with stable angina and obstructive coronary artery disease

Treatment (%)	Women (n=1,638)	Men (n=4,402)	P-value
Revascularisation	66	76	<0.001
Antithrombotics	95	93	0.004
Aspirin	88	85	0.004
Beta-blockers	72	74	0.101
Calcium antagonists	48	43	0.001
ACE/ARB	49	50	0.366
Statins	91	90	0.153

Conclusions: Women with stable angina and obstructive CAD were less likely to receive invasive treatment compared with men. Unlike results from recently published studies this was not explained by differences in age or extent of coronary artery lesions. Furthermore, women were not less treated with secondary prophylactic cardiovascular medication.

5957 | BEDSIDE
A comparison of ESC and NICE guidelines for patients with suspected CAD: evaluation of the pre-test probability risk scores in clinical practice

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Introduction: The ESC (2013) and UK NICE (2010) have published guidelines for investigating patients with suspected coronary artery disease (CAD). Both guidelines provide a risk score (RS) to assess the pre-test probability for CAD derived from the Diamond/Forrester and Duke databases. The ESC RS is based on age, gender and typicality of pain, whilst NICE, in addition to this, differentiates patients into "low" and "high" risk groups depending upon pre-existing risk factors for CAD.
Aim and methods: Our aim was to establish whether there was a difference between these RS. We retrospectively reviewed 376 consecutive patients seen in RACP clinic between 2010-2014. The RS was calculated using both ESC and NICE guidelines and compared.
Results: From the 376 patients 227 (60.4%) were male and the mean age was 59.5 years. The mean RS was greater using NICE guidelines compared to ESC across all variables. The mean RS was 19.7% greater using NICE (p<0.001). Females had slightly greater mean RS difference, 21.6% compared to 18.5% in males. Amongst patients with typical chest pain (n=101), the difference between the RS was 12.1% compared to 22.2% for atypical chest pain (n=266) (p<0.001). When we divided the cohort based on NICE risk criteria into "'high" and "low" risk groups, the difference in the RS was 23.9% in the "high" risk group (n=309) (p<0.001) compared to 0.3% in the "low" risk group (n=67).
In patients who underwent stress echocardiography those with positive results (n=14) had a RS difference of 17.0% (91.6% vs. 74.6%; NICE vs. ESC) compared to 20.4% (65.4% vs. 45.0%) with negative results (n=107). In patients who underwent myocardial perfusion scintigraphy those with positive results (n=24) had a RS difference of 24.3% (76.3% vs. 52.0%) compared to 20.9% (66.6% vs. 45.7%) with negative results (n=31). In patients who underwent cardiac CT those with moderate/severe disease (n=17) had RS difference of 12.5% (69.2% vs. 56.7%) compared to 14.8% (63.4% vs. 48.6%) with normal/mild disease (n=88).
Conclusion: Our results show that there is significant difference between the two risk score models. The risk score was significantly higher when calculated using the UK NICE model across all subgroups. Moreover, both guidelines overestimate the prevalence of CAD however, the ESC guidelines appear to do this to a lesser extent. This overestimation is likely to be due to the fact that the risk scores were developed on tertiary centre patients and don't apply to our primary care populations. Refining the risk scores in subsequent guidelines will be critical as this determines the choice of investigation.

FUNCTIONAL CHARACTERISTICS IN CARDIOMYOPATHY

5968 | BEDSIDE
Combination of global longitudinal strain and late gadolinium enhancement predicts left ventricular reverse remodeling in patients with non-ischemic dilated cardiomyopathy

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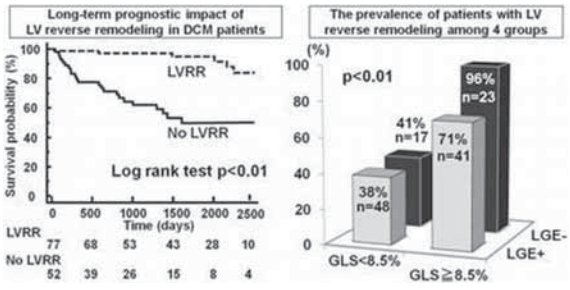
Purpose: In non-ischemic dilated cardiomyopathy (DCM), left ventricular reverse remodeling (LVRR) is a marker of a favorable prognosis, and has been reported to be predicted by the absence of late gadolinium enhancement (LGE) in cardiac magnetic resonance (CMR). The aim of this study was to investigate whether global longitudinal strain (GLS) by two-dimensional speckle-tracking echocardiography (2DSTE) has a predictive value for LVRR in combination with LGE in DCM patients.
Methods: We studied 129 consecutive patients with DCM (age 59±15 years, 88 males, LV ejection fraction (EF) 32±8%). All patients underwent CMR and echocardiography with conventional assessment including left atrial (LA) volume and mitral regurgitation (MR) grade and with 2DSTE analysis. After the optimal medical therapy for 12 months, echocardiography was repeated for assessment of LVRR which defined as an absolute increase in LVEF ≥10% accompanied by a decrease in LV end-diastolic volume ≧10%. Cardiac death and heart failure hospitalization were defined as cardiac events.
Results: LVRR was observed in 76 patients (59%), significantly associated with LGE, LA volume, MR grade, and GLS (all p<0.05), and strongly associated with a favorable long-term outcome (Follow-up period 1585±835 days, 29 cardiac events, p<0.01). Multivariate regression analysis showed that GLS was an independent predictor of LVRR (OR: 1.20, 95%CI: 1.07-1.34, p=0.003). Dividing all patients into 4 groups with LGE and GLS cut-off value of 8.5% derived from ROC curve analysis, we found the significant deference in the prevalence of patients with LVRR among them (p<0.01).



Conclusions: GLS is significantly associated with LVRR, particularly predicts LVRR in combination with LGE, and can indicate a favorable outcome in DCM patients.

5969 | BEDSIDE

Characterisation of transmural longitudinal and circumferential mechanics by multi-layer strain analysis in hypertrophic cardiomyopathy

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Purpose: Until recently, the application of two-dimensional speckle-tracking (2DSTE) in asymmetric hypertrophic cardiomyopathy (HCM) has been hampered by the impossibility to adjust the region of interest (ROI) to the variations in LV wall thickness.
This study aimed to characterize the transmural mechanics in HCM pts using a novel software which allows multi-layer strain analysis and an adjustable ROI.
Methods: In 40 HCM pts and 40 controls matched for age, gender, body size and LVEF, longitudinal (LS) and circumferential (CS) strain at LV endo-, mid- and epicardial layers were analyzed using EchoPAC BT13 (GE Vingmed, N). Global and segmental transmural gradients (LSepi-endo and CSepi-endo) were calculated. LVEF and mass were measured by 3D echo.
Results: In HCM pts, global LSendo, LSmid and LSepi were significantly impaired with respect to controls ($p<0.001$), and were inversely correlated with LV mass (r=0.60, r=0.65 and 0.67, $p<0.001$). LSepi-endo was similar in HCM pts vs controls (5.9±1.5% vs 5.4±0.9%, p=0.11). While CSendo was similar, CSepi was significantly lower in magnitude in HCM pts (Table), and was related with LV mass (r=0.57, p=0.001). Thus, CSepi-endo was larger in pts vs controls (20.8±5.4% vs 14.5±3.2%, $p<0.001$). At ROC curve analysis, LSendo, LSmid and LSepi (AUC 0.90-0.92), and CSepi and CSepi-endo (AUC 0.84 for both) had the best discriminatory power to separate HCM pts from controls.

Multi-layer CS in HCM vs controls

		HCM pts	Controls	p
LV base	CSendo	–34.5±6.1	–33.8±4.4	0.582
	CSmid	–24.1±4.8	–26.4±3.4	0.045
	CSepi	–17.1±4.6	–20.7±3.3	0.001
LV mid	CSendo	–36.1±6.0	–34.4±4.5	0.245
	CSmid	–24.9±4.9	–26.9±3.2	0.085
	CSepi	–17.9±4.2	–21.2±2.6	0.002
LV apex	CSendo	–48.2±15.9	–46.1±9.0	0.554
	CSmid	–30.5±13.0	–35.1±6.2	0.084
	CSepi	–21.3±10.4	–28.8±4.8	0.001

Conclusions: Multi-layer strain analysis with adjustable ROI may provide objective insights into HCM pathophysiology and disease course. Characterisation of transmural mechanics appeared to be more advantageous for CS than for LS.

5970 | BEDSIDE

Usefulness of speckle myocardial imaging modalities for the differential diagnosis of left ventricular non-compaction of the myocardium

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Introduction: Current diagnostic criteria for left ventricular non-compaction (LVNC) may result in overdiagnosis of this disease. Analysis of strain and left ventricular (LV) rotation have reported abnormal results in patients (pts) with LVNC. In our study we evaluate the role of speckle imaging (strain and rotation) in the differential diagnosis of LVNC.
Methods: We have included in our study all pts that between January 2012 and February 2014 fulfilled currently accepted echocardiographic criteria for LVNC in a tertiary hospital non-invasive cardiology laboratory. A control group of healthy individuals was created after gender and age adjustment. Speckle-tracking echocardiography was performed in both groups and morphologic, functional, strain and rotation variables were analysed.
Results: We identified 21 pts fulfilling current criteria for LVNC. Among them, 11 had an ejection fraction (EF) <50% (33%±11) with mean age of 54±15 years. Ten pts aged 39±13 had an EF≥50% (59%±2). The control group consisted of 21 individuals aged 45±15. Pts with LVNC and EF<50%, had as compared with controls a larger LV (52±7 mm vs 42±6, $p<0.05$), larger left atrial diameter (LA) (39±7 mm vs 32±5, $p<0.05$), reduced e' (7±3 cm/s vs 14±4, $p<0.05$), and reduced global longitudinal strain (GLS) (-13±3 vs -18±2, $p<0.05$). LVNC pts with EF≥50% did not show significant differences in comparison with controls, but presented a smaller LA (32±5 vs 39±7, $p<0.05$), smaller LV (44±4 vs 52±7, $p<0.05$), higher GLS (-18±3 vs -13±3, $p<0.05$), higuer e' (12±4 cm/s vs 7±3, $p<0.05$), and were younger, compared to those with LVNC and EF<50%. All but one pts with LVNC and EF<50%, showed an abnormal LV rotation. This abnormal pattern was observed in 2 pts (20%) of LVNC with EF≥50%, and in none of the controls. In pts with LVNC, EF ≥50%, and abnormal rotation, GLS was lower than in controls, next to significance (-16±1 vs -18±2, p 0.1). This difference was not observed in pts with LVNC, EF≥50%, and a normal rotation pattern (-19±3 vs -18±2, p NS).
Conclusions: Our pilot study suggests that among pts fulfilling the morphologic criteria of LVNC, speckle myocardial imaging techniques could be useful in differentiating between healthy individuals (having hypertrabeculated, but functionally normal LV, with a physiological LV rotation and strain) and pts presenting some myocardial functional abnormalities in spite of a preserved EF. Although data on the clinical evolution of these pts must be acquired in the future it might be worth considering the inclusion these functional parameters into the diagnostic criteria of LVNC, reducing the rate of overdiagnosis.

5971 | SPOTLIGHT

Progression of cardiomyopathy in familial amyloid polyneuropathy - impact on prognosis

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Introduction: The cardiomyopathy in familial amyloid polyneuropathy (FAP) V30M-TTR is due to progressive infiltration of amyloid in the heart causing diastolic dysfunction in the early stages and myocardial thickening in the more advanced stages of the disease. The temporal evolution and the prognostic significance of these changes are not well known.
Aims: To analyze the progression of cardiomyopathy by conventional echocardiography and to determine its prognostic impact.
Methods: Prospective study of consecutive V30M-TTR mutation carriers followed annually with echocardiography and conventional Doppler. The predictive value of echocardiography in the risk of death from any cause was evaluated by multivariate Cox regression analysis with adjustment for age and Kaplan-Meier survival analysis (considering multiple tests per patient).
Results: A total of 220 patients (45±14 years, 54.1% female) were followed for a median of 56 months and performed 745 tests. With aging there was a progressive increase in the thickness of the septum and posterior wall, in the left atrium dimension, in the A wave velocity, in the E wave deceleration time and in the pressure half-time and a decrease in the E/A ratio. With the increase in symptoms duration, similar changes were observed. The risk of death increased by 13% for each 1 mm increment of the septal wall (HR: 1.127, 95% CI 1.059 -1.198, $P<0.001$). The presence of diastolic dysfunction (E/A ratio <1 or >2.5) improved the accuracy of prognostic stratification. The risk of death duplicated in patients with septal thickness ≥12 mm (HR: 2.112, 95% CI 1.119-3.986, P=0.021) and it was four times higher in those with concomitant diastolic dysfunction (HR: 4.783; 95 2.863 to 7.990%, $P<0.001$) as compared to patients with septal thickness <12 mm.
Conclusion: In patients with FAP V30M-TTR, the progression of cardiomyopathy is associated with increased risk of death. The combination of septal thickening and diastolic dysfunction increases significantly the risk.

5972 | BEDSIDE

Consistency of independent estimates between two assessors of 2D global strain by a novel multi-layer analysis technique using transthoracic echocardiography in HCM with preserved LV ejection fraction

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Purpose: To evaluate the consistency with which different assessors estimated two-dimensional (2D) left ventricular global longitudinal (GLS) and circumferential strain (GCS) by a novel multi-layer analysis technique using transthoracic echocardiography (TTE), we acquired data from hypertrophic cardiomyopathy (HCM) subjects with preserved LV ejection fraction (EF).
Methods: A total of 22 HCM subjects (16 male, 61±15 yrs, LV EF >50%) underwent TTE (Vivid E9, GE Healthcare) to measure 2D multi-layer global strain in LV myocardium using ECHOPAC software. Apical 4-, 2-, and 3-chamber views were acquired for GLS and parasternal short-axis views at the level of mitral valve, papillary muscle, and apex were acquired for GCS. Quantitative strain measurements of 1) all layers, 2) endocardial myocardial layer only and 3) epicardial myocardial layer only, were performed for both GLS and GCS.
Results: Correlation coefficients (CC) of estimates of 2D GLS in all layers, endocardial and epicardial layers at 4-, 3- and 2-chamber views by the two assessors were 0.872, 0.829, 0.862 (4-chamber view), 0.679, 0.561, 0.742 (2-chamber view), and 0.866, 0.817, 0.878 (3-chamber view), respectively. CC of estimates of 2D GCS in all layers, endocardial and epicardial layers at the level of mitral valve, papillary muscle, and apex by the two assessors were 0.471, 0.478, 0.487 (mitral

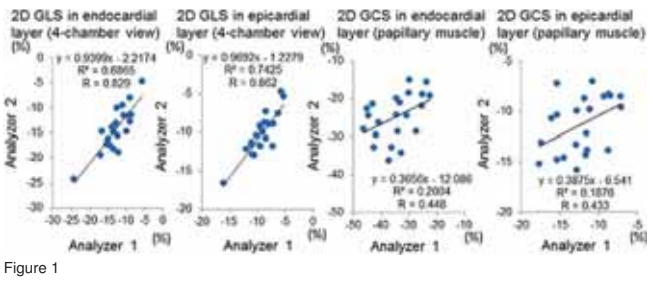

Figure 1

valve), 0.448, 0.448, 0.433 (papillary muscle), and 0.870, 0.743, 0.822 (apex), respectively.
Conclusions: Consistency of independent estimates of 2D GLS in all layers, endocardial and epicardial layers using TTE was better than for 2D GCS in all layers, endocardial and epicardial layers in HCM subjects with preserved LV EF.

PLATELETS AND THROMBOSIS

5977 | BENCH
Uridin triphosphate (UTP) and its analogue are potent antagonists for platelet and endothelial P2Y12 receptors: effect on platelet aggregation and endothelial barrier

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Background: Platelets express two ADP receptors namely P2Y1 and P2Y12 which regulate ADP and agonist-induced platelet shape change and aggregation, respectively. Moreover, we have found that human endothelial cells also express both P2Y1 and P2Y12 receptors. The aim was to characterise the pharmacological profile of the P2Y12 receptor for uridine triphosphate (UTP) and its analogue 2-thio UTP (S-UTP) in platelets and human endothelial cells.
Methods: The study was carried out on platelet rich plasma freshly isolated from blood donated by healthy human volunteers and freshly isolated human umbilical vein endothelial cells (HUVEC).
Results: Both UTP and S-UTP inhibited ADP-induced platelet aggregation in a conc.-dependent manner, S-UTP being more potent. The IC50 values against ADP (10 μM)-induced platelet aggregation were 32±9 and 0.36±0.05 μM for UTP and S-UTP, respectively. Likewise, both nucleotides potently antagonised collagen (2 μg/ml)- and epinephrine (10 μM)-induced platelet aggregation. However, both UTP and S-UTP had no effect on ADP- and MRS2365 (P2Y1 receptor agonist)-induced platelet shape change suggesting their inactivity at P2Y1 receptors. PCR data showed that HUVEC also express both P2Y1 and P2Y12 receptors. ADP reduced basal as well as antagonised thrombin-induced endothelial hyperpermeability in a conc.-dependent manner with IC50 8±2 μM. This barrier protective effect of ADP was abolished with a specific P2Y1 receptor antagonist (MRS2500; 10μM) suggesting a P2Y1 receptor-dependent phenomenon. Both UTP and S-UTP increased endothelial cAMP levels and antagonised thrombin-induced hyperpermeability by 30±5% and potentiated the barrier protective effects of ADP. Similar results were obtained when a specific P2Y12 receptor antagonist (AR-C66096; 10 μM) was employed or P2Y12 receptors were knocked down using shRNA viral plasmids.
Conclusion: The novel data demonstrate that UTP and S-UTP are potent P2Y12 receptor antagonists and inhibit agonist-induced platelet aggregation as well as thrombin-induced endothelial hyperpermeability. Moreover, ADP mediates endothelial barrier protective effect via activation of P2Y1 receptors and this effect can be potentiated by inhibition of P2Y12 receptors.

5978 | BEDSIDE
Gremlin-1 is released by platelets and its expression level correlates with the degree of platelet activation in patients with coronary artery disease

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Background: Gremlin-1 is a member of the DAN-protein family, a subdivision of the cysteine knot superfamily. Through its interaction with Slit proteins Gremlin-1 regulates monocyte chemotaxis. Furthermore Gremlin-1 is an endogenous inhibitor of MIF and modulates vascular inflammation and atherosclerosis. Platelets play a central role in atherogenesisand have been shown to be a major source of pro-atherogenic chemokines. In the present study we analyzed therefore the expression and release of Gremlin-1 from resting and activated platelets in patients with stable coronary artery disease (CAD).
Methods: Weanalyzed 222 patients with CAD undergoing PCI. Using Western blot analysis and FACS we showed that Gremlin-1 is highly expressed by resting and activated human platelets. Platelet aggregation was assessed using Muliplate Analyzer®.
Results: We found that expression of Gremlin-1 on platelets' surface was independent from platelet count (mean platelet count: 250, platelet-bound Gremlin-1: 14,8±7,0 vs. 17,7±7,5, p=0,987). Platelets activated with ADP showed a higher expression of Gremlin-1compared to resting thrombocytes (14,866±7,27 vs. 14,76±6,20, t-test fir Equality of Means p=0,000). Platelets, which showed a high expression of P-selectin (cut-off 5,5),appeared to express also higher amounts of Gremlin-1 on their surface (14,9±6,2 vs. 10,4±2,6; p=0,039). Diabetes mellitus, the presence of an acute coronary syndrome and an impaired left ventricular function also correlated with a significantly higher expression of Gremlin-1 in platelets (diabetes: 15,4±8,8 vs. 14,6±6,4; p=0,018; ACS: 16,1±8,2 vs. 13,7±6,1; p=0,036; impaired left ventricular function: 14,83±8,5 vs 13,8±5,8; p=0,035) compared to controls. The amount of platelet-bound Gremlin-1 did not significantly vary depending on the degree of platelet aggregation (r=0,49, p=0,571). The platelet-bound expression of GREM1 was not influenced by a therapy with P2Y12-inhibitors (14,95±6,8 vs 14,6±10,1; p=0,16), aspirin (14,2±6,3 vs 15,4±7,9; p=0,08) or oral anticoagulation (14,8±7,3 vs. 15,3±7,6; p=0,43).
Conclusion: Gremlin-1 is carried and released by platelets. Its expression level depends on the degree of platelet activation, suggesting platelets as an unrecognized source of Gremlin-1 in acute and chronic cardiovascular diseases. Gremlin-1 might therefore be used as a marker for thrombocyte activation in patients with stable CAD or ACS independent from anti-platelet treatment or platelet count

5979 | BENCH
Secretion of the proinflammatory signaling lipid sphingosine-1-phosphate from human platelets depends on the multidrug-resistance protein (MRP)-4 and is inhibited by statins

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Purpose: Activated platelets secrete the immunomodulatory lipid mediator sphingosine-1-phosphate (S1P). Numerous biological functions such as inflammation, cell migration and survival are regulated by S1P. The underlying release mechanism may involve ATP-dependent transport. A potentially involved transport protein is the multidrug-resistance protein (MRP)-4 (ABCC4), which is highly expressed in platelets. Several statins are substrates for MRPs and affect platelet function. Therefore, we investigated the contribution of MRP4 to the secretion of S1P from human platelets and a possible interference by statins.
Methods: Transport of S1P was investigated in isolated inside-out membrane vesicles of Sf-9 insect cells transfected with human MRP4 and in human platelets. S1P was determined by mass spectrometry, MRP4 by Western blotting. Localization studies of platelet MPR4 and S1P were performed by confocal microscopy.
Results: Transport studies with fluorescein-labeled S1P indicated a significant ATP-dependent uptake into MRP4-enriched membrane vesicles compared to basal transport rates into vesicles from mock-transfected Sf-9 cells. In addition, ATP-dependent transport of S1P was determined in membrane vesicles prepared from human platelets. The expression of MRP4 in platelets was confirmed by Western blotting. Detection of fluorescein-labeled S1P together with staining of MRP4 by a specific antibody in confocal fluorescence microscopy revealed a partial co-localization of S1P and MRP4 in human platelets. Incubation of MRP4-expressing vesicles from Sf-9 cells with fluvastatin or rosuvastatin (1 - 100 μM) resulted in a significant reduction of S1P transport, suggesting competition with this transport pathway. Furthermore, both statins also inhibited S1P release from human platelet activated with the thromboxane receptor agonist U46619 (10 μM) or with thrombin receptor activating peptide (100 μM).
Conclusions: Secretion of S1P from activated platelets depends on MRP4 and statins can interfere with this transport process. Potentially, this mechanism may contribute to the known pleiotropic anti-inflammatory effects of statins.

5980 | BENCH
Rivaroxaban, a direct factor Xa inhibitor, attenuates neointima formation following vascular injury in the mouse through the inhibition of proliferative activation of vascular smooth muscle cells

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Background: Activated factor X (FXa) is a key member in the coagulation cascade responsible for thrombin generation, although accumulating evidence suggests it also has various biological functions in many cell types, contributing to the pathogenesis of neointima formation after vascular injury. In this study, we assessed the hypothesis that rivaroxaban, a direct FXa inhibitor, attenuates neointima formation after vascular injury in mice through the inhibition of proliferative activation of vascular smooth muscle cells (VSMCs).
Methods and results: C57BL/6 mice were subjected to wire-mediated vascular injury. Rivaroxaban (5 mg/kg/day) or vehicle (control) was administered orally for 4 weeks after injury. The cross sections of the injured arteries at four weeks were stained with elastica van Gieson (EVG) to evaluate neointima formation. There were no differences in body weight gain, blood pressure, plasma glucose levels and plasma lipid levels between the groups. Rivaroxaban significantly reduced neointima area (30452±2531 μm^2 vs. 19582±2531 μm^2; $P<0.05$) and intima/media ratio (4.37±0.50 vs. 2.60±0.50; $P<0.05$) compared with control group. There was no difference in cross sectional area of media between the groups (9460±1729 μm^2 vs. 10214±1729 μm^2; P=0.76). In vitro experiments using rat VSMCs demonstrated that FXa stimulation increased mRNA expression of Krupple-like transcription factor 5 (KLF-5), which is known as one of the key molecules regulating VSMC proliferation.
Conclusion: Rivaroxaban attenuates progression of neointima formation in a mouse model of vascular injury. Our analyses suggest that FXa contributes to proliferative activation of VSMCs at least partially, participating in the progression of neointima formation after vascular injury.

5981 | BENCH
High density lipoprotein from patients with coronary heart disease loses anti-thrombotic effects on endothelial cells: impact on arterial thrombus formation

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Background: Primary prevention studies demonstrated an inverse relation between HDL levels and the incidence of cardiovascular events. However, recent evidence suggests that HDL is impaired under certain conditions. HDL from healthy subjects exerts anti-thrombotic properties. Whether this is also the case for HDL from patients with stable coronary heart disease (CHD) or acute coronary syndrome (ACS) is unknown.
Methods: HDL was isolated from healthy subjects or patients with stable CHD or ACS by sequential ultra-centrifugation. Analysis of endothelial tissue factor (TF), tissue factor pathway inhibitor (TFPI), plasminogen activator inhibitor type-1 (PAI-1) and tissue plasminogen activator (tPA) expression was performed by Western blot analysis or ELISA. Arterial thrombus formation was analysed in a murine carotid artery photochemical injury model.
Results: In human aortic endothelial cells in culture, HDL (50 μg/ml) from healthy subjects (HS) inhibited thrombin-induced TF expression and activity, while HDL from CHD and ACS patients did not. Similarly, only healthy HDL increased endothelial TFPI expression and tPA release, while HDL from CHD and ACS patients had no effect. Healthy HDL inhibited thrombin-induced PAI-1 expression, while HDL from ACS patients enhanced endothelial PAI-1 expression. Inhibition of nitric oxide (NO) formation with L-NAME (100 μmol/L) abolished the anti-thrombotic effects of healthy HDL on TF, TFPI, and tPA expression. The nitric oxide donor, DETANO, mimicked the effects of healthy HDL and counterbalanced the loss of anti-thrombotic effects of HDL from CHD and ACS patients in endothelial cells. In line with this observation, healthy HDL, but not HDL from CHD and ACS patients, increased endothelial NO production. In the laser-injured carotid artery of the mouse, thrombus formation was delayed in mice treated with healthy HDL compared with mice treated with vehicle or HDL from patients with CHD or ACS. Analysis of tissue lysates demonstrated that treatment with HDL from HS but not from patients with stable CHD and ACS inhibited TF and PAI-1 activity. Analysis of platelet activation by whole blood aggregometry demonstrated no significant difference in platelet aggregation capacity in response to thrombin between the different groups.
Conclusion: HDL from CHD and ACS patients loses the ability of healthy HDL to suppress TF and to increase TFPI and t-PA and instead enhances PAI-1 and arterial thrombus formation. This effect is mainly related to the disability of HDL from patients with coronary heart disease to stimulate NO production in endothelial cells.

5982 | BENCH
Influence of reconstituted HDL (rHDL) on activation of platelet G-protein coupled receptors (GPCR) in coronary artery disease

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Background: Thienopyridines such as clopidogrel are irreversible P2Y12-receptor inhibitors which are efficient for the prevention of ischemic events in atherosclerotic diseases like coronary artery disease (CAD). Though, there are various hints for impaired response to Clopidogrel due to various causes. The activity of the G-protein coupled P2Y12 receptor is dependent on a special membrane structure, so called lipid rafts. Amongst others, these rafts are modulated by HDL (high density lipoprotein).
We investigated whether P2Y12-receptor inhibitor response is modulated by endogenous HDL-levels in patients with CAD and if modulation of response can be achieved by substitution of reconstituted HDL (rHDL).
Methods: HDL was measured in CAD patients with ST-elevation myocardial infarction and regarded in respect of PRI levels (platelet reactivity index = indicator for quality of response to P2Y12-receptor inhibitors). Moreover, reconstituted HDL was generated and in vitro experiments were performed including flow cytometry, aggregometry and western blotting.
Results: In CAD patients we found an inverse association of clopidogrel responsiveness with HDL (T= –2.1, p=0.040; PRI for HDL below median 62.6±4.0%, PRI for HDL above median 53.1±4.8%, $p<0.05$) indicating an influence of endogenous HDL levels on P2Y12-receptor activity. Furthermore, PRI was detected by flow cytometry before and after in vitro incubation of whole blood with rHDL. A significantly reduction of PRI levels was observed after addition of 100μg/ml rHDL ($p<0.05$). Light transmission aggregometry showed a significantly reduced area under the curve (AUC) following ADP stimulation after incubation of platelet rich plasma (PRP) with different concentrations of rHDL ($p<0.05$ for 100μg/ml rHDL). Moreover, a significant reduction in AKT-pathway signal transduction was observed after incubation of samples with rHDL and subsequent stimulation with ADP ($p<0.05$ for rHDL 100μg/ml + 200μg/ml). Therefore, washed platelets from patients suffering from coronary artery disease were generated.
Conclusion: The platelet membrane structure composition is important for receptor function. Substitution of rHDL seems to be beneficial for platelet integrity. Particularly in coronary artery disease, this could be of special interest in the face of minor response to P2Y12 receptor inhibitors.

PERIPHERAL ARTERY DISEASE: HIGHER BURDEN, MORE SOLUTIONS

6010 | BEDSIDE
High prevalence and urban-rural comparisons of peripheral artery disease in the elderly in Central Africa: the EPIDEMCA study

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Purpose: Data on the epidemiology of peripheral artery disease (PAD) in Central Africa are sparse and limited to some urban areas. Given the particularities of the urban-rural socio-economical gradient in these countries, we sought to determine the prevalence and risk factors of PAD in Republic of Congo (ROC) and Central African Republic (CAR) and compare these data in rural and urban populations in each country.
Methods: This cross-sectional study, was performed in two predefined districts representative of Brazzaville (ROC) and Bangui (CAR) (sampling proportional to the size of the main subdivisions in Brazzaville and Bangui) and by exhaustive door-to-door sampling in two rural areas (Gamboma (ROC) and Nola (CAR)). All individuals ≥65 years living in these areas were invited to participate. Socio-demographic data, medical history, medication, clinical (brachial blood pressures and ankle-brachial index (ABI), body mass index, waist and hip circumferences) and biological data (blood glucose, C-reactive protein and total cholesterol) were collected. We defined PAD when ABI ≤0.90.
Results: Among the 2113 eligible subjects, 110 declined participation, and 131 excluded because of missing data. The remaining 1871 participants (Brazzaville=439 and Gamboma=493 in ROC, Bangui=476 and Nola=463 in CAR) composed our study population (mean age: 73.1±6.6 yrs, 61.9% females). In the whole cohort, the prevalence of PAD was 14.8%, higher in ROC than in CAR (17.4% vs. 12.2%, p=0.0071) and higher in females than males (16.6% vs. 11.9%, p=0.0122). Overall, PAD rates increased with age, respectively at 10.9%, 14.9%, 15.1% and 22.2% for age bands of 65-69, 70-74, 75-79, 80+ yrs ($p<0.01$). The urban/rural difference in PAD rates was significant in ROC (urban 20.7% vs. rural 14.4%, p=0.0114) but not in CAR (11.5% vs. 12.9%, p=ns). In multivariate analysis in the whole cohort, PAD was significantly associated with age (OR: 1.03; 95%CI: 1.01-1.06, p=0.0039), dyslipidemia (OR: 1.88; 1.23-2.88, p=0.0034), smoking (OR: 1.78; 1.22-2.56, p=0.0026), obesity (OR: 1.98; 1.05-3.70, p=0.0336), as well as undernutrition (OR: 1.49; 1.06-2.09, p=0.0226), whereas regular alcohol consumption was inversely correlated with PAD (OR: 0.73; 0.40-0.99, p=0.0437).
Conclusion: This largest epidemiological study in Africa highlights the elevated prevalence of PAD in the elderly, especially in females. In ROC, where the urban-rural socio-economic gradient is more pronounced, PAD was found significantly more frequent in the urban zone. Our data support the epidemiological transition of African countries, more visible in the urban population.

6011 | BEDSIDE
Effect of statin treatment after endovascular therapy for femoropopliteal lesion

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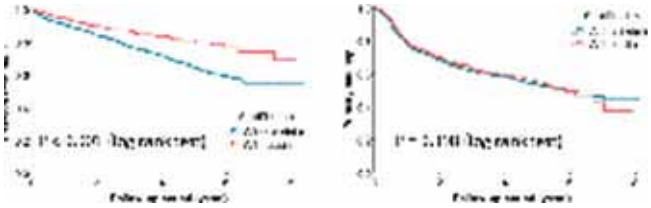
Background: Statin treatment decreases cardiovascular events by reducing LDL cholesterol and inflammation. However, long term effects for peripheral artery disease (PAD) are little known. The purpose of this study is to survey statin treatment may affect PAD patients with femoropopliteal artery disease after endovascular therapy (EVT).
Methods: A multicenter retrospective analysis of femoropopliteal intervention between January 2004 and December 2011, 3469 limbs from 2740 patients were studied. The primary endpoint was major adverse cardiac events (MACE), defined as a composite of death / myocardial infarction (MI)/ stroke, and secondary endpoint was primary patency (defined as treated vessel without restenosis).
Results: Mean follow-up period was 28.0±22.2 months. 1021 patients (37.2%) were treated with statin. Freedom from MACE at 5 years was 81.2% in statin group and 63.8% in no statin group, $p<0.001$, respectively. Primary patency rate at 5 years was 51.7% and 51.2%, p=0.398, respectively. After adjusting all variables, statin treatment significantly improved MACE [hazard ratio (HR) 0.800, 95% confidential interval (CI) 0.643 - 0.995, p=0.045]. And there was no sig-

nificant difference about failure of primary patency [hazard ratio (HR) 0.956, 95% confidential interval (CI) 0.822 - 1.113, p=0.564].



Kaplan-Meier curve, statin for FP lesion.

Conclusions: Statin treatment for PAD patients with femoropopliteal artery lesions is effective for reducing the cardiovascular events. However, there is not significant effect for vessel patency after EVT.

6012 | BEDSIDE
Below-the-ankle artery run-off; A predictor of technical success and mortality for critical limb ischemia

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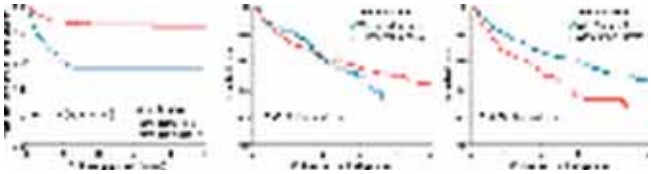
Aims: Endovascular therapy for critical limb ischemia (CLI) still continues to develop for limb salvage and to improve the prognosis. However, it is unclear whether diseased level affects limb prognosis and mortality.
The purpose of this study is to survey how the existence of the below-the-ankle (BA) artery run-off affects for CLI patients after isolated below-the-knee (BK) interventions.
Methods: A multicenter retrospective analysis of BK intervention done for CLI between March 2004 and October 2010, 790 limbs from 689 patients with tissue loss CLI due to isolated BK lesions were studied. They were divided for two groups. One was with BA (1 or 2 run-off) group, and the other was without BA (0 run-off) group. The main endpoint was freedom from amputation, and secondary endpoint was survival rate.
Results: Mean follow-up period was 19.0±17.7 months. There was a significant difference between two groups about technical failure (7.9% in BA run-off group and 18.4% in without BA run-off group, $p<0.001$). By multivariate analysis, without BA run-off was a significant predictor of technical failure [hazard ration (HR) 2.35, 95% confidential interval (CI) 1.44-3.81, $p<0.05$]. In addition, technical failure was a significant predictor of major amputation [HR 2.61, 95% CI 1.44-3.81, $p<0.05$]. However, there was no significant difference for survival rate about technical success and failure (p=0.485). Without BA run-off was a predictor for mortality [HR 1.44, 95% CI 1.08-1.91, $p<0.05$].



Kaplan-Meier curve, technical and BA.

Conclusions: The existence of the BA artery run-off is an important predictor for endovascular technical aspect and mortality. Technical success improves limb prognosis. However, Impact for survival rate is not technical success but the existence of BA run-off for CLI patients.

6013 | BEDSIDE
Comparison of treatment modalities for femoropopliteal lesion in claudicants

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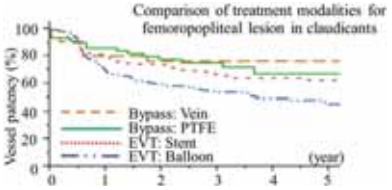
Objectives: Although endovascular therapy (EVT) has advanced, outcome of treatment for femoropopliteal artery disease is still not enough. There is still limited information regarding differences between EVT and Bypass surgery for femoropoplieteal desease. The purpose of this study is to evaluate long-term outcomes of EVT (with or without stent) and bypass surgery (vein or PTFE graft) in claudicant with femoropoplieteal desease.
Methods: Data from the RECANALISE (REtrospective Comparative ANAlysis of the revascuLarization method for Infrainguinal artery diseaSE, surgical reconstraction and Endovascular treatment) registry, retrospective, multicenter registry in our country (n=1308), was analyzed. In 589 claudicants with femoropopliteal lesion, bypass surgery (n=91) was performed with vein (n=32) or PTFE (n=59) graft, balloon angioplasty (n=203) or stent replacement (n=295) was used in case of EVT (n=498). We evaluated each group by Kaplan-Meier methods and compared by the log rank test.
Results: 1 and 5 years primary patencies were 82% and 74% in bypass group; 68% and 51% in EVT group. According to log rank test, primary patency rates of bypass group with PTFE or vein graft were significantly higher than EVT group with stent.



Outcome of each treatment modality.

Conclusions: In conclusion, bypass surgery is feasible treatment for the claudicant with femoropoplieteal desease. Stent placement is better solution in case of EVT for femoropoplieteal lesion.

6014 | BEDSIDE
Patients with rutherford classification IV have different characteristics and outcome, compared with V and VI

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Background: Endovascular treatment (EVT) has been progressing as the first-line treatment for critical limb ischemia (CLI). Patients with resting leg pain without ulcer or gangrene (Rutherford classification IV: R-4) are classified CLI, but they might have different characteristics compared with Rutherford classification V and VI (R-5/6). Our study aims were to estimate the clinical differences between R-4 and R-5/6 and also to find risk factors for EVT outcomes in R-4.
Methods: Based on the data obtained from a multi-center retrospective study, 1332 limbs (R-4: 331 limbs, R-5/6: 1001 limbs), those were undergone EVT as the primary treatment for isolated infra-popliteal disease at 14 hospitals in Japan between March 2004 and December 2012, were analyzed.
Results: For patients' backgrounds, there were significant differences between R-4 and R-5/6 groups, in age (74 vs. 71 years, $p<0.0001$), body mass index (22.3 vs. 21.6, p=0.0101), ambulatory status (76.1% vs. 54.6%, $p<0.0001$), dyslipidemia (38.1% vs. 30.6%, p=0.0334), diabetes mellitus (61.3% vs. 75.3%, $p<0.0001$), end stage of renal disease (54.4% vs. 66.0%, p=0.0016), and heart failure history (17.1% vs. 31.3%, p=0.0004). For lesions' characteristics, Transatlantic Inter-Society Consensus (TASC) proportion (AB/CD: 21/310 vs. 28/973, p=0.0075) and a presence of below the ankle disease (45.8% vs. 67.3%, $p<0.0001$) had significant differences. Angiographic and clinical EVT success rate in R-4 group was significantly higher (97.6% vs. 90.4%, $p<0.0001$) and both freedom rate from major adverse limb event (MALE: 10.0% vs. 20.1%, p=0.0004) and amputation free survival rate (40.6% vs. 57.7%, $p<0.0001$) were also better in R-4 group during the mean follow up period (658 days). No significant predictors in patients' backgrounds and lesions' characteristics for freedom from MALE were analyzed but limbs that obtained initial EVT success had kept free from MALE more than EVT failed limbs (93.1% vs. 50%, $p<0.0001$) in R-4 group.
Conclusion: From the present results, patients classified R-4 should be recognized to have quite different backgrounds from R-5/6. And once initial EVT obtained clinical success, they could keep free from MALE in such subset of CLI.

6015 | BEDSIDE
Endovascular therapy of steno-occlusive subclavian and innominate artery disease: safety and efficacy in a large cohort at a single center institution with over 20 years experience

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Background: Revascularization of atherosclerotic lesions of the subclavian or innominate artery can be accomplished either by surgical or endovascular therapy. In the recent past, endovascular procedures became increasingly favoured over surgical procedures due to their minimally invasive character and low rate of complications especially in patients with significant cardiovascular comorbidities. Therefore, the main aim of this study was to determine the safety and outcome

of endovascular therapy for steno-occlusive subclavian or innominate artery disease at a large single-center institution over a long time period of more than two decades.

Patients and methods: We retrospectively analyzed all endovascular procedures of stenosis or occlusion of the subclavian or innominate artery at both sites of our institution between January 1990 and October 2013.

Results: During the observation period, a total of 130 procedures were attempted in 127 mostly symptomatic patients with stenosis (n=108; 83%) or occlusion (n=22; 17%) of the subclavian (n=119; 92%) and innominate (n=11; 8%) artery. The overall technical success rate was 97.7% (n=127/130). Accounting for the type of lesion, the success rate for stenosis was 100% (n=108/108) and for total occlusion 86% (n=19/22). The periprocedural complication rate was low and included stroke, transient ischemic attacks, and access site complications of 0.8%, 1.5%, and 3.8%, respectively.

During a mean follow up of 28 months (range 1-207 months) the rate of restenosis (>70%) was 12%. Apart from recurrence of symptoms, which was a significant predictor of restenosis (p=.008), no further significant lesion or procedural risk factor for the development of restenosis could be identified.

Conclusions: Data from this large cohort of typical clinical patients demonstrate that stenosis and occlusion of the subclavian and innominate artery can be treated safely and successfully by endovascular therapy with excellent long-term patency.

ACUTE HEART FAILURE: UPDATE 2014

6024 | BEDSIDE
Does diagnostic position of Acute Heart Failure (AHF) have relationship to mortality? - a report from Euro Heart Failure survey-1

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Introduction: Heart failure is a common problem in elderly population that is almost always associated with other serious co-morbid conditions. Majority of previous publications reporting deaths and discharges with heart failure focused only on those patients with heart failure as a primary discharge diagnosis, which is likely only to be a minority of cases.Failure to quantify the size of the problem is likely to lead to an under-estimate of the health economic impact of heart failure and under-provision of resources for its care.

Methods: EHFS1 screened consecutive deaths and discharges during 2000-2001 primarily from medical wards over a 6 week period in 115 hospitals from 24 countries, to ascertain patients with known or suspected HF. Information on presenting symptoms and signs were gathered. Mortality was assessed during hospital admission and then 3 months after discharge

Results: Of all 10,701 patients admitted with suspected HF, Heart failure was considered to be the primary reason for admission in 4,234 (40%), secondary reason for admission if complicated or prolonged stay in further 1,772 (17%), and in 4, 695 (43%) it was uncertain that HF is actively contributing in index admission. Patients admitted with secondary heart failure were older 74 years verses 72 in primary HF and 73 in uncertain group. 71% from primary HF, 52% from secondary HF and 58% from uncertain group were on loop diuretic. 58% from Primary HF, 51% from secondary HF and 41% from uncertain group had moderate to severe left ventricle systolic dysfunction. 278 (16%) from secondary HF, 286 (9%) from primary HF and 183 (4%) from uncertain group were died during index hospital admission. According to cox regression analysis Hazard ratio of death in secondary HF group was 3.26 (P= <0.001, CI 2.7-3.93) and Primary HF 1.72 (P= <0.001, CI 1.43-2.08) compare to uncertain group during index admission. Total death after 12 weeks of discharge were again higher in secondary HF, 389 (22%), 558 (13%) in primary and 412 (9%) in uncertain group.

Conclusion: HF as a secondary diagnosis carries a high mortality. Suspected but unconfirmed HF is not benign and probably reflects a mixture of patients with a heterogeneous prognosis, including those with inadequately investigated HF, patients with other serious medical problems and inappropriate loop diuretic use.

6025 | BEDSIDE
Sex differences in new-onset heart failure patients with reduced and preserved ejection fraction

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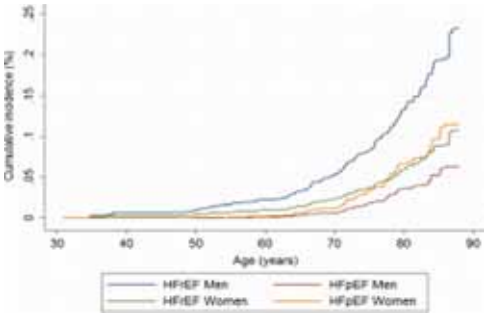
Purpose: In cohorts of patients with heart failure, females more often have HFpEF, while males more often have HFrEF. However, sex differences in the incidence and risk for heart failure have not been well described. We analyzed sex differences in heart failure development.

Methods: We studied 8592 subjects (50.1% women; mean age: women 48.1 years, men 50.4 years) of the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, examining sex differences in the incidence of heart failure with reduced and preserved ejection fraction (HFrEF <40% and HFpEF >50%).

Results: During a median follow up of 12.5 years, 133 women and 241 men developed heart failure. Incidence rates per 1000 person-years in women compared to men were lower for HFrEF (1.2% vs. 3.0%; P<0.001), but higher for HFpEF (1.2% vs. 0.7%; P<0.001). Women developed HFpEF later in life than HFrEF (mean age: 75.1 vs. 69.7 years; P=0.033), while no significant age difference was detectable for men (mean age: 72.2 vs. 69.5 years; P=0.116). Multivariable competing risks analyses for HFrEF, HFpEF and all-cause mortality showed women had lower risk for HFrEF (subhazard ratio = 0.47; 95% CI 0.29-0.76, P=0.002) and higher risk for HFpEF (subhazard ratio = 1.99; 95% CI 1.12–3.56, P=0.020) compared with men. Atrial fibrillation as a risk marker for the development of HFpEF in women, but not in men (P-for interaction = 0.030).



Cumulative incidence of HF by type & sex.

Conclusions: Compared to men, women have a lower risk of developing HFrEF and a higher risk of developing HFpEF, the latter manifesting at higher age, and being associated with atrial fibrillation.

6026 | BEDSIDE
Elevated heart rate and in-hospital mortality in acute heart failure

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Background: Heart failure (HF) poses a unique medical burden of high morbidity and mortality. Elevated resting heart rate is associated with worse outcomes in chronic HF but little is known about its prognostic impact in acute setting.

Methods and results: We examined the association of heart rate with in-hospital mortality in a cohort of 778 patients admitted for acute HF between January 2010 and December 2012. None of the patients had significant arrhythmias, required invasive ventilation, or presented with acute coronary syndrome or primary valvular disease. Heart rates was obtained 24-36 hours after admission. Forty patients died during the hospital stay. Those patients were older (78±9 vs. 72±12 years; p=0.0021), had higher heart rate (92±22 vs. 78±18 bpm; p<0.0001), NT pro-BNP (p=0.0005), creatinine (18±18 vs. 14±10 mg/dL; p=0.023), were often diabetics (p=0.026) and had lower systolic and diastolic blood pressures (p<0.05). With multivariable analysis, age (p=0.008), heart rate (p<0.0001), and creatinine (p=0.024) emerged as independent predictors of in-hospital mortality. The mortality rate was higher in patients with a heart rate >80 bpm (11% vs. 3%; p<0.01).

Variables	Whole Cohort (n=712)	Survivors (n=672, 94%)	Death (n=40, 5.6%)	p
Age, years	72±12	72±12	78±9	0.0021
Male gender, n (%)	425 (60)	396 (59)	29 (73)	0.089
Heart rate, bpm	79±18	78±18	92±22	<0.0001
Systolic BP, mmHg	121±24	122±24	113±30	0.046
Diastolic BP, mmHg	68±13	68±13	58±16	0.0002
LV ejection fraction, %	44±16	44±16	46±15	0.46
Medical history				
Hypertension, n (%)	331 (46)	314 (47)	17 (42)	0.17
Diabetes, n (%)	132 (17)	118 (17)	14 (35)	0.026
COPD, n (%)	177 (25)	166 (25)	11 (27)	0.96
Prior MI, n (%)	129 (18)	125 (19)	4 (10)	0.08
Prior HF, n (%)	204 (29)	194 (29)	10 (25)	0.28
Laboratory findings				
Hemoglobin, g/L	12±2	12±2	12±2	0.63
NT-proBNP, pg/mL	9615±12872	8488±10660	24692±26433	0.0005
Creatinine, mg/dL	14±11	14±10	18.5±18	0.023
Sodium, mmol/L	140.7±4.4	141±4.2	140±6.3	0.71

Conclusions: Higher heart rate 24-36 hours after admission for acute HF is associated with increased risk of in-hospital mortality. Early targeting of elevated heart rate might represent a complementary therapeutic challenge.

6027 | BEDSIDE

Mechanical circulatory support with the Impella 5.0 and intra-aortic balloon pump for cardiogenic shock in acute myocardial infarction. The IMPELLA-STIC study

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Background: Cardiogenic shock is associated with high mortality in patients with acute myocardial infarction (AMI). Adding a left ventricular assist device (LVAD) to an intra-aortic balloon pump (IABP) may help to bridge patients to recovery from left ventricular failure.
Objectives: This multicentric study aimed to test whether the LVAD Impella LP5.0 associated with an IABP provides superior hemodynamic support compared with IABP alone.
Methods: This was a prospective, randomized study. The primary end point was the change in cardiac power index (CPI) from baseline to 12 hours after implantation. Secondary end points included lactic acidosis change from baseline to 96 hours and mortality after 30 days. Difference of CPI between 12 hours and baseline was compared between groups using Mann-Whitney test.
Results: Fifteen patients with cardiogenic shock were randomized and 13 were available for analysis. In 13 patients the allocated device (n=6 IABP, n=7 Impella LP5.0+IABP) could be safely placed. No patient died before the implantation. Baseline characteristics were similar in both groups.
The CPI after 12 hours of support was increased but not significantly in patients with the Impella LP5.0+IABP compared with patients with IABP (LP5.0+IABP: ΔCPI = 0.08$\pm$0.08 watt/m^2; IABP: ΔCPI = -0.02$\pm$0.25 watt/m^2; p=0.415). Overall 30-day mortality was 28.6% (2 deaths one week after inclusion) in the Impella LP5.0+IABP group compared to none in the IABP group. There was no difference between groups for lactic acidosis.
Conclusions: In patients presenting with cardiogenic shock caused by AMI, the use of the Impella LP 5.0 and IABP provided no superior hemodynamic support compared to intra-aortic balloon pump alone.

6028 | BEDSIDE

Nesiritide in heart failure: post ASCEND-HF and ROSE-AHF meta-analysis and systematic review

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Background: The use of nesiritide for the treatment of acute decompensated heart failure (ADHF) patients has been controversial due to questions raised on its comparative high cost and side effects. Earlier meta-analyses on nesiritide produced contradictory results. We aim to investigate the clinical outcomes including mortality, haemodynamic and renal effects of nesiritide treatment on patients with ADHF.
Method: We searched multiple databases, without language restrictions, to identify pertinent studies published from January 1996 to March 2013. We selected randomized, controlled trials that compared nesiritide with standard treatment, control or placebo to treat patients with ADHF that provided mortality data.
Results: This meta-analysis has included eleven trials and a total number of 9242 patients with results published between 1996 and 2013. Specifically, it has added data from the four most recent relevant studies including ASCEND-HF and ROSE-AHF studies. There were no significant differences found on 30 day all-cause mortality and readmission, odds ratio (OR): 0.96 (95% CI: 0.77, 1.19) and 0.95 (95% CI: 0.66, 1.36) respectively. The OR for hypotension was significantly higher in the nesiritide group OR: 2.54 (95% CI: 1.62, 4.00). We also found a small but significant rise in the risk of worsening renal function for the nesiritide group OR: 1.30 (95% CI: 1.04, 1.62).
Conclusion: Use of nesiritide for treatment of AHF did not improve clinical outcomes but increased risk of worsening renal function. Nesiritide has no role in the management of acute heart failure.

6029 | SPOTLIGHT

Global trends in hospitalization and mortality in acute heart failure: economic burden and the need for innovation in disease management and healthcare policy

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Purpose: To evaluate the burden of disease due to acute heart failure (AHF) and highlight the need for evidence-based policy recommendations to improve quality of care and reduce deaths of patients with AHF.
Methods: Medical literature and government databases were searched for data on hospitalizations, re-hospitalizations, deaths and economic costs attributable to heart failure (HF) in Europe and the USA since 2000. An international panel of HF experts identified barriers to improving care and consensus recommendations for policy change.
Results: The table shows published or retrieved hospitalization data for HF as a primary diagnosis. Published values for in-hospital mortality due to HF ranged from 2.8% to 11.1%; those for mortality within 1 year of admission ranged from 17.4% to 36.2%. Readmission rates were in the range 22.1–26.9% (30 days) and 27.2–67.0% (1 year). In 6 of 8 countries investigated, hospitalizations for HF had increased during the past decade. Estimates of economic costs of heart failure were 1–2% of total healthcare budget. Available evidence indicated variation in the quality of care among hospitals and regions. The need for rapid diagnosis and treatment, the heterogeneity of precipitating factors and the typical repeated episodes of decompensation and resulting complex patient trajectories were identified as significant challenges by the expert group.

HF hospitalizations (primary diagnosis)

Country (year)	N	N/total	Length of stay (days)	Country (year)	N	N/total	Length of stay (days)
Austria (2010)	25,370	1.0%	7.3	Poland (2012)	10,425	1.9%	8
England (2011-12)	61,130	0.4%	7	Spain (2011)	63,754	1.8%	7.46
France (2008)*	148,292	–	9.9	Sweden (2011)	33,550	2.2%	6.43
Germany (2007)	335,000	2.0%	–	Switzerland (2011)	14,398	1.1%	–
Netherlands (2010)	29,760	1.5%	–	USA (2007)	982,000	2.9%	5.3
Norway (2008)	8,735	1.1%	–				

N, number of hospitalizations; N/total, N as a percentage of total admissions (including planned); *Primary or secondary HF diagnosis.

Conclusion: AHF imposes a substantial and increasing burden on healthcare resources and society. Policy recommendations identified to improve care and reduce mortality included optimizing patient care transitions, improving patient education and support, providing equity of care for all patients, appointing experts to lead HF care, developing and implementing better measures of care quality, and promoting HF prevention.

VENOUS THROMBOEMBOLISM: WHAT'S NEW?

6034 | BEDSIDE

Venous thromboembolism management in European countries: Baseline characteristics, risk factors, and comorbidity data from the PREFER in VTE Registry

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Background: In Europe there are over one million venous thromboembolism (VTE) events annually. However, for this major health problem, there is a paucity of data on the current real-life case-mix and management.
Methods: The PREFER in VTE registry enrolled the first patient in January 2013. Enrollment is ongoing until March 2014. Centres in France, Germany, Switzerland, Austria, Italy, Spain and UK (33% office-based/67% hospital-based) are participating. We collected patient characteristics, pulmonary embolism (PE)/deep vein thrombosis (DVT) presentation at time of diagnosis, and management information at baseline and after 1, 3, 6 and 12 months after baseline. Here, we report a snapshot of the available baseline data.
Results: 1843 evaluable VTE patients (mean age 61.6 y, 47.7% female) participated in this analysis 62.8% had DVT and 37.2% suffered from PE with recurrent VTE making up 18.2% of the cohort. Risk factors included cancer, varicose veins, prolonged immobilization, major surgery/trauma and thrombophilia. Common cardiovascular comorbidities were comparable within both groups. Bleeding events in the three months prior to diagnosis were recorded in 4.4%, 25.9% were major, 51.9% were clinically relevant non-major. Gastrointestinal and intracerebral bleeds made up 32.1% and 14.8% of all bleeds, respectively (Table).

Table 1. Risk factors and comorbidity data from the PREFER in VTE Registry

	Total Cohort	DVT only	PE only	DVT and PE
History of cancer	18,2%	17,7%	16,9%	20,8%
Prolonged immobilisation	18,3%	16,9%	19,5%	21,5%
Varicose veins	22,3%	24,5%	17,6%	19,3%
Surgery/trauma	14,1%	13,5%	14,6%	15,6%
Hypertension	44,8%	41,6%	53,9%	46,9%
Vascular disease	8,1%	6,9%	9,4%	10,9%
Chronic venous insufficiency	19,2%	20,2%	19,2%	16,2%
Renal insufficiency	6,9%	6,6%	10,4%	4,8

Conclusions: PREFER in VTE describes the breadth of real-life patients with VTE in office and hospital practice within Europe. Risk factors for VTE and cardiovascular disease are common in VTE patients. Unlike clinical trial populations, over 4% of VTE patients have had a bleeding event in the 3 months prior to diagnosis. These factors need to be considered in therapeutic pathways.

6035 | BEDSIDE
Cost-effectiveness of apixaban compared to other anticoagulants for the acute (6-month) treatment of venous thromboembolism

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Purpose: The AMPLIFY trial compared apixaban to low-molecular-weight heparin (LMWH) followed by warfarin for acute treatment and prevention of venous thromboembolism (VTE) over a six-month period. Two other novel oral anticoagulants (NOACs), dabigatran (initiated after parenteral anticoagulant therapy) and rivaroxaban, have also been studied for this indication. This analysis evaluated the cost-effectiveness of apixaban compared to other NOACs and LMWH/warfarin from the perspective of the UK National Health Service.
Methods: A Markov model was developed to evaluate the lifetime clinical and economic impact of six-month treatment of patients following a VTE event with apixaban versus other NOACs and LMWH/warfarin. A network meta-analysis was conducted to compare apixaban to other NOACs and LMWH/warfarin for the following end-points: recurrent VTE and related deaths, major bleeds, clinically relevant non-major bleeds, myocardial infarction, and ischemic stroke. Outcomes were life years gained, quality-adjusted life years gained (QALYs), and costs estimated in 2012 GBP. Cost and health outcomes were discounted at 3.5% per year.
Results: Six-month treatment with apixaban following a VTE event was predicted to increase life expectancy and QALYs versus dabigatran, rivaroxaban, and LMWH/warfarin over a lifetime horizon. Apixaban was associated with cost savings versus dabigatran and rivaroxaban, dominating these treatments in cost-effectiveness analysis. Apixaban was a cost-effective alternative to LMWH/warfarin at an ICER of approximately £7,000/QALY. One-way sensitivity analyses indicated that model conclusions were robust over a wide range of inputs. Probabilistic analysis demonstrated that apixaban had the highest probability of being the most cost-effective treatment at willingness-to-pay threshold of approximately £9,000 per QALY.

Cost-effectiveness of apixaban

Comparator	Δ Costs	Δ QALYs	ICER (cost/QALY) for apixaban vs. comparator
Dabigatran	–£63	0.020	Dominant
Rivaroxaban	–£5	0.005	Dominant
LMWH/warfarin	£156	0.022	£7,136/QALY

Conclusions: Six months of apixaban for acute treatment and prevention of VTEs appears to be a dominant alternative to other NOACs and a cost-effective alternative to current standard of care comprising LMWH/warfarin.

6036 | BEDSIDE
Use of statins and the risk of recurrent venous thromboembolism

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Background: There is evidence that statins may decrease the risk of incident venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), but data on the risk of recurrence of VTE is limited.
Aim: To determine the effect of statin use on the risk of recurrent VTE in patients with incident VTE.
Methods: We identified a cohort of 25,681 men and women aged 65 years and older diagnosed with incident VTE between January 1, 1994 and December 31, 2004, who were followed until December 31, 2005, using the linked administrative healthcare databases of the province of Québec, Canada. Time dependent Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of recurrent VTE associated with post-incident VTE use of statins. Effect modification by pre-incident VTE use was considered.
Results: During a mean follow up of 2.95 years (standard deviation 3.04), 2,343 recurrent VTE events occurred. Post-incident VTE use of statins was associated with a decreased risk of VTE recurrence (HR 0.75; 95% CI, 0.63-0.89).The decreased risk of recurrent VTE was more pronounced with increasing duration of statin use post-incident VTE (continuous use between 0 and 6 months, HR 0.84 95% CI, 0.69-1.01; 6 to 12 months, HR 0.63 95% CI, 0.44-0.91; $\geq$12 months, HR 0.50 95% CI, 0.34-0.74, p-value for trend $<$0.001). Similar reduction in risk of recurrence was observed with high potency and low potency statin use (HR 0.72; 95% CI, 0.54-0.96 and HR 0.76; 95% CI, 0.63-0.91, respectively). The use of statins prior to incident VTE did not modify the association between post-incident VTE use and recurrent VTE. Similar risk reductions were seen in patients with DVT with or without PE, and in those with PE alone.
Conclusion: Statin use after diagnosis of incident VTE was associated with a decreased risk of recurrent VTE. Our study supports the need for a trial to assess the efficacy and safety of statins in the long-term management of VTE.

6037 | BEDSIDE
Comparison of apixaban, dabigatran and rivaroxaban in the acute treatment and prevention of venous thromboembolism: systematic review and network meta-analysis

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Purpose: Anticoagulation with low molecular weight heparin and vitamin K antagonists is the current standard of care (SOC) for venous thromboembolism (VTE) treatment and prevention. Although the novel oral anti-coagulants (NOACs) have been compared with SOC in this indication, no head-to-head randomised controlled trials (RCTs) have compared the NOACs directly. A systematic review and network meta-analysis (NMA) were conducted to compare the efficacy and safety of the NOACs for the acute treatment and prevention of VTE.
Methods: Electronic databases (accessed December 2013) were systematically searched to identify RCTs evaluating apixaban, dabigatran and rivaroxaban versus SOC. Eligible patients included adults with an objectively confirmed deep vein thrombosis (DVT), pulmonary embolism (PE) or both. A fixed-effect Bayesian NMA was conducted for outcomes of interest.
Results: Five phase III RCTs met criteria for inclusion: apixaban [AMPLIFY (n=5,395)]; rivaroxaban [EINSTEIN-DVT/PE pooled (n=4,832+3449]; dabigatran [RE-COVER I/II (n=2,539/2568)]. The relative risk of 'VTE and VTE-related death' was lower with apixaban compared with both dabigatran (↓23%) and rivaroxaban (↓7%) (Table 1). Apixaban treatment was associated with the most favourable safety profile of the NOACs, showing a statistically significantly reduced risk of 'major or clinically relevant non-major (CRNM) bleed' compared with rivaroxaban (↓53%) and dabigatran (↓31%). Rivaroxaban was associated with significantly increased risk of major or CRNM bleed compared with dabigatran (↑48%).

Table 1. NMA results

Outcome	Relative risk (95% CrI)		
	Apixaban vs Dabigatran	Apixaban vs Rivaroxaban	Rivaroxaban vs Dabigatran
VTE and VTE-related death	0.77 (0.47, 1.27)	0.93 (0.60, 1.46)	0.82 (0.52, 1.31)
Major or CRNM bleed	0.69 (0.51, 0.94)*	0.47 (0.36, 0.61)*	1.48 (1.15, 1.89)*
Major bleed	0.40 (0.19, 0.81)*	0.55 (0.27, 1.09)	0.73 (0.40, 1.31)
CRNM bleed	0.80 (0.57, 1.12)	0.47 (0.36, 0.62)*	1.70 (1.28, 2.25)*
All-cause mortality	0.79 (0.44, 1.40)	0.82 (0.50, 1.34)	0.97 (0.58, 1.60)

CrI, credible interval. *Statistically significant.

Conclusions: While the NOACs have a similar efficacy in terms of a reduction in VTE or VTE-related death, apixaban reports a significantly better safety profile in terms of reduction in major or CRNM bleed for acute treatment and prevention of VTE.

6038 | BEDSIDE
Impact of a multifaceted intervention to prevent venous thromboembolic disease in patients admitted to emergency ward and hospitalized for acute medical illness: a multicentre cluster randomized trial

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Purpose: Despite evidence-based guidelines for venous thromboembolism (VTE) prevention, many hospitalized patients in medical setting do not receive appropriate prophylactic treatment. We hypothesized that a multifaceted intervention in the emergency wards could improve adherence to guidelines and decrease the rate of symptomatic VTE or major bleedings during the 3 months following a hospitalization for an acute medical illness.
Methods: We performed a prospective cluster-randomized trial in 27 emergency wards. All consecutive patients aged over 40 years, admitted for an acute medical illness and not receiving curative anticoagulant treatment. After a pre-intervention period during which baseline practices were observed, centers were randomized between an active recommendations implementation group (n=13) and a control group without intervention (n=14). The intervention consisted of meetings with emergency physicians and reminders (rounds, posters, pocket cards) to im-

plement prophylactic anticoagulant treatment when indicated. We measured the rate of symptomatic VTE (pulmonary embolism, deep venous thrombosis or unexplained sudden death) or major bleedings during a formal 3-month follow-up after hospital admission (primary outcome). The secondary outcomes were symptomatic VTE, major bleedings and the adequacy of thromboprophylaxis (in terms of indication and conditions). An independent adjudication committee blinded of group assignment assessed all outcomes. We estimated odds ratios (OR) by using a mixed-effect logistic regression with the center as random intercept.
Results: We included 14760 patients for the main outcome and 16753 for the practice adequacy analysis (preintervention period: 1403 and intervention period: 15351). The 3-month rate of symptomatic VTE or major bleedings was 3.1% (464/14760) with no difference between the intervention group and the control group (adjusted OR: 1.02 (95%CI, 0.78 – 1.34)). The rates of VTE (1.9%) and of major bleedings (1.3%) were similar in both groups. The proportion of patients who received adequate prophylaxis did not differ between the pre-intervention period and the intervention period, in the intervention group (52.4% vs. 50.9%) and in the control group (49.1% vs. 48.8%).
Conclusion: Only half of the patients hospitalized for acute medical illness received adequate VTE prophylaxis. Meetings and reminders in emergency wards did not improve guidelines adherence and did not change the 3-months rate of symptomatic VTE or major bleedings.

6039 | BEDSIDE
Strategies and timing of the search for malignancies in patients with deep vein thrombosis during the hospital stay and post-discharge; a single center retrospective analysis

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Objective: Unprovoked deep vein thrombosis (DVT) are related to malignant diseases, therefore diagnostic procedures are recommended for patients (pts.) with unprovoked DVT, but the timing and the extent of the diagnostic procedures is not defined.
Material and methods: In this retrospective study the medical charts of 599 pts. (mean age 63.2±17.2 years; 49.6% male), who were admitted to an hospital from 2006 to 2008 with the diagnosis of a DVT were analyzed for differences in the extent of the search for malignancies between different medical specialties and for possible trigger mechanisms leading to an extended diagnostic strategy during the hospital stay. The pts. and their general practitioners were contacted to describe the extent and timing of diagnostic procedures and the findings after the hospital stay.
Results: Of the 599 pts., 124 had a known malignancy at the time of the DVT. Predictors for a search for malignancies during the hospital stay were age, the extent of the DVT and the classification as unprovoked or as recurrent DVT. A new malignancy was diagnosed in 22 pts. during the hospital stay; in 8 pts. during a second hospital stay in between the next 6 months. Most of the tumors were detected with CT-scans; only 5 with a simple diagnostic strategy with biplane chest X-ray and/or abdominal ultrasound. Follow up could be realized in 378 of these pts. with no malignancy diagnosed at discharge. The diagnostic strategies post discharge were independent of the diagnostic tests during the hospital stay. There were no DVT related predictors detectable for the initiation of diagnostic procedures or the extent of the search for tumors post-discharge. Another 31 malignancies were detected post discharge, 49% of these during the first year and 71% during two years post-discharge. Most of the tumors could be detected by physical examination, as stated by the general practitioners. Only 58% of the DVTs of these patients were initially classified as unprovoked.
Conclusions: Only half of the malignancies in pts. with acute DVT are diagnosed during the hospital stay. Diagnostic strategies for search of malignancies should include CT-scans and repeated reevaluation of the patients in the first months after the DVT, but redundant examination post-discharge should be avoided. The classification of provoked and unprovoked DVT is not a valid discriminator for the choice of the diagnostic strategy.

UNRESOLVED ISSUES IN THE TREATMENT OF SYNCOPE

6062 | BENCH
Limited utility of physical counterpressure manoeuvres in preventing syncopal recurrence in patients older than 40 years with recurrent neurally-mediated syncopes. an analysis from the issue-3 trial

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Background and purpose: Physical counter-pressure manoeuvres are effective in young patients with vasovagal syncope and recognizable prodromal symptoms. Aim of this study was to investigate their effectiveness in patients ≥40 years with severe neurally mediated syncope (NMS) enrolled in the Third International Study on Syncope of Uncertain Etiology (ISSUE-3).
Methods and results: In the ISSUE-3 study, 63 out of 162 patients had a diagnosis of hypotensive NMS (type 2,3 and 4A) documented by implantable loop recorder (ILR); of these, 40 were instructed to perform isometric leg and arm physical counter-pressure manoeuvres (PCM) therapy. Their mean age was 62±13 years; 71% of patients had a history of some episodes without prodrome. A group of 45 untreated patients acted as controls. During follow-up, syncope recurred in 15 PC patients (39%) and in 24 control patients (53%). At 21 months, the estimated product-limit syncope recurrence rates were 42% (95%CI 29-62) and 64% (95%CI 48-80) respectively (p=0.30).
Conclusions: The benefit of PC manoeuvres was limited in ISSUE-3 patients affected by hypotensive NMS. The likely factors that hampered effectiveness of PC therapy were older age and absence of sufficiently long recognizable prodromal symptoms in the ISSUE-3 population.

6063 | BEDSIDE
Fluoxetine vs placebo for the treatment of recurrent vasovagal syncope associated with anxiety

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Purpose: The optimal medical therapy of patients with vasovagal syncope (VVS) remains controversial. Since "stress" is commonly associated with recurrent syncopal episodes and serotonin reuptake inhibitors (SSRIs), such as fluoxetine, exhibit central nervous system actions, we aimed at examining whether fluoxetine exerts beneficial effects relative to placebo in their ability to prevent VVS in the subset of pts with psychosocial distress.
Methods: We assessed 105 pts with typical history of recurrent VVS (at least 2 episodes during the preceding 6 months), without other comorbidities, mean aged 48±5 years, 36 males/24 females, all with a typical history of VVS and a diagnostic, positive head-up tilt test (HUT). Their psychological, stress-related profile was assessed by the Anxiety Sensitivity Index (ASI) questionnaire, a simple, 16-item questionnaire, assessing fear of anxiety-related sensations, previously studied in VVS (D' Antono, 2009). Patients scoring positive for ASI (n=60) were randomized in a 2:1 way to receive either 10-40 mg fluoxetine daily (n=40) or placebo (n=20), and were followed for 1 year. Log-rank test was used to compare the time to recurrence of syncope between the 2 groups. Only syncopal episodes occurring after the first month of treatment were included in the analysis.
Results: Following a 12-month follow-up period, a significant difference was observed between pts receiving fluoxetine and those with placebo treatment, regarding the distribution of syncope-free time during the study period (log rank test $p<0.05$). A significant difference was also observed between the 2 groups regarding the total number of patients who experienced syncope during follow-up: 5/40 (12.5%) of pts with fluoxetine vs 9/20 (45%) pts with placebo, $p<0.05$.
Conclusion: Fluoxetine is superior to placebo in VVS associated with anxiety and may be a first-line pharmacological treatment in this difficult-to-treat subgroup of patients with VVS.

6064 | BEDSIDE
Use of midodrine for patients with reflex syncope, single-centre results in 178 patients

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Background: Reflex syncope is the most common cause of transient loss of consciousness, T-LOC. Occasionally practical manoeuvres may help symptoms, but many patients need something more to sustain normal life. We report the use of open-label midodrine, an a-agonist, in the treatment of this common problem.
Objectives: To examine the effect of midodrine in patients with reflex syncope in routine clinical practice in an arrhythmia clinic and Rapid Access Blackouts Triage Clinic.
Patients: We treated 178 patients, 140 female (78%), 38 male, (22%) patients with midodrine. Mean age was 40±18, (range 16- 90. 72 patients were under 30. All patients had had episodes of T-LOC, for a duration of 49±55 months at first appointment. Thirty nine patients had previously been misdiagnosed with epilepsy.
Data Collection and Analysis: All patients had to have the drug prescribed and dispensed from the base-hospital, because midodrine is not licensed in the UK. For similar reasons, all had regular and frequent follow-up offered, which documented dosage, compliance and number and frequency of syncopes. Patients typically started on 2.5mg tds, and were titrated upwards until symptoms resolved or side-effects prevented a further increase. All patients had a 12-lead ECG.
Results: Follow up data were available for 167 patients (93%), and 11 were lost to follow-up. 156 patients had a normal ECG. 118 patients (66%) showed improvement in symptoms, (syncope reduction from 19±18 to 02±06 per 6 months and of these 51 (28%) patients had complete resolution of symptoms. 41 (23%) patients had been on sodium tablets, and 37 (21%) had been on fludrocortisone without improvement. 16 (9%) patients were able to stop treatment when symptoms resolved completely after 52±42 months of treatment. 13 (7%) patients could only tolerate a minimum dose of midodrine, (2.5mg tds), 17 (9%) had to stop midodrine because of side effects. 15 (8%) patients had no response at all, Conclusion: In

a large open-label observational series of patients with a clinical diagnosis of Reflex Syncope, midodrine treatment resulted in complete resolution of syncope in 28%, and significant clinical benefit in 66%. In recent years randomised controlled studies have shown no benefit for b-blockers and fludrocortisone. Reflex syncope is a very difficult syndrome to treat, and midodrine shows promise.

6065 | BENCH
Prognostic value of very prolonged asystole during head-up tilt test

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Purpose: To evaluate the frequency and prognosis of a cardioinhibitory response with a very prolonged asystole (>30 seconds) during head-up tilt (HUT) test.
Methods and results: Dual-centre retrospective study, including a total of 2210 consecutive HUT tests (with pharmacological sensitization with isosorbide dinitrate) performed in 2194 patients with syncope of unknown etiology, between January/2003 and October/2013.
Cardioinhibitory response with asystole was observed in 145 (6.6%) of these tests [44.1% women, mean age 39±20 years old, 168 (7.6%) in the non-pharmacological phase], with a median duration of asystole of 10 [6-19] seconds. Very prolonged asystole (>30 seconds) was documented in 10 patients (50% women; mean age 41±20 years; 1 (10%) in the non-pharmacological phase, after 9 minutes of tilt). The longest pause lasted 63 seconds. In all patients avoidance of triggering factors and physical counterpressure maneuvers were recommended. Telephone follow-up was performed (median follow-up of 47 [24-69] months): in one patient, fludrocortisone was started, but discontinued after 10 months on the patient's own initiative (no symptomatic improvement); tilt training was conducted in 1 patient and none received a pacemaker. Three patients (30%) had syncopal recurrences (median number of syncopes 1.67±1.16), but with no significant trauma, and no patient died.
Conclusion: In our study, very prolonged asystole was rare (0.5%) and prognosis, in terms of syncopal recurrence and mortality, was benign despite a non-aggressive management.

6066 | BEDSIDE
A long-term follow-up of patients with prolonged asystole > 15secs on head-up tilt testing

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Purpose: Head up tilt testing (HUT) is often used for the diagnosis of vasovagal syncope (VVS), and can provoke a cardioinhibitory response. VVS is a significant cause of syncope and is usually considered benign having little or no effect on mortality and quality of life. We sought to characterise the long-term outcomes of patients with prolonged asystole (>15s) on HUT. We describe the longest duration follow-up of patients with prolonged asystole on HUT.
Methods: In 2012, we conducted a retrospective study on patients found to have prolonged asystole >15s on HUT identified from 5133 patients who were investigated between 1999-2012 at our institution. Patients were mailed questionnaires or telephoned directly to ascertain outcomes. Where contact was not initially possible, the patients' general practitioners were contacted directly to ask for up-to-date contact details. Statistical analysis was performed using unpaired two-tailed Student's t-test.
Results: A total of 26 (62% male) patients with a mean age of 45±18 years and a mean duration of asystole on HUT of 26±7s (range 17-45s) were successfully followed-up from a total of 77 patients identified. The follow-up duration was 99±39 months. Six of the 26 patients had undergone permanent pacemaker (PPM) implantation. Of the remaining 20 patients, 16 reported improved symptoms spontaneously. Ten patients sustained injury prior to HUT while only 3 patients sustained injury after HUT. There were no major injuries or deaths after HUT. The 6 patients that had undergone PPM implantation had a mean age of 68±13 (67% male), with 5 of these patients being over 60 at the time of follow up. 4 patients had no further syncope after PPM implantation, with 2 having an improvement but still suffering with recurrent syncope. 51 patients could not be contacted by mail, telephone, or had moved without giving new contact details to their previous general practitioner. The high rate of patients lost of follow up was because patients were referred to our tertiary centre from a wide area and were not necessarily seen after HUT. These patients represented the younger cohort with a mean age of 35±16, they were therefore more likely to move place of residence. The mean duration of asystole in these patients was not different (26.5±8.5s, P = ns).
Conclusion: Prolonged asystole (>15s) on HUT does not necessarily predict adverse outcomes with most patients improving spontaneously over a long-term period. Pacemaker insertion does not abolish syncopal symptoms in all patients.

6067 | BEDSIDE
A permanent pacemaker is often not the correct treatment for unexplained syncope and symptoms versus ECG correlation is crucial for correct decision-making

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Introduction: Syncope is traditionally associated with bradyarrhythmias, such as AV block and sinus arrest/asystole, and in those patients a permanent pacemaker may be an appropriate treatment. However, syncope may also occur with tachyarrhythmias, that need other specific treatment, or in the absence of any arrhythmia.
Methods: The observational multicenter PICTURE registry provided an opportunity to assess the mechanism of unexplained syncope by means of an implantable loop recorder (ILR), that provided symptoms–ECG correlation by means of automatic or patient activated ECG capture, with both modes programmable at the investigator's discretion. A total of 570 patients received an ILR (Reveal) and were followed until recurrence or for at least one year. A device-captured ECG was available in 175 of the 218 patients with a recurrence of syncope, while there was no capture in 43 patients. Bradyarrhythmias included asystole >3s, bradycardia <40 bpm and AV block; tachyarrhythmias included both ventricular and supraventricular tachycardias.
Results: In the 175 patients, syncope was associated with bradyarrhythmias in 95 (54%) patients, tachyarrhythmias in 50 (29%) patients, both brady- and tachyarrhythmias in 12 (7%) and no arrhythmia was found in 33 (19%) patients. A permanent pacemaker was implanted in 86%, 20%, 67% and 0%, respectively; an ICD in 4%, 18%, 25% and 0%; catheter ablation was performed in 1%, 14%, 8% and 0%; drug therapy given in 4%, 28%, 17% and 15%; education/counseling provided in 2%, 6%, 0% and 24%, and no treatment was prescribed in 6%, 22%, 1% and 55%. Brady- and tachyarrhythmias were diagnosed with patient activation in 15% and 26%, respectively; auto-activation in 45% and 34%, and with both modes in 40% and 40%.
Conclusion: While almost all patients with bradyarrhythmias were eventually implanted with a permanent pacemaker, as many as 48% had an arrhythmia mechanism that required other treatment, if any. If a pacemaker had been implanted based on symptoms alone, a large proportion of patients would have received inappropriate treatment. The ILR provided proof of the underlying mechanism of syncope which made specific treatment possible, whether pharmacological and/or non-pharmacological.

Poster Session 7

PUBLIC HEALTH AND HEALTH POLICY

P6069 | BEDSIDE
Impact of premature myocardial infarction in the family: cardiovascular disease and medication use before and after a premature myocardial infarction in a first-degree relative

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Purpose: A premature myocardial infarction (MI, <55 years in men, <65 years in women) in the family is a dramatic event that may prompt first-degree relatives to seek medical advice about their own disease risk. However, the health profile of this group is unknown. In a cohort of MI-free persons with premature MI in a first-degree relative, we assessed the incidence of cardiovascular disease indicators before and after the sentinel MI.
Methods: Using national registers, we identified index persons with a premature MI in the period 1977-2012. We then identified a cohort of first-degree relatives alive and MI-free at the time of the index person's MI (IP-MI). We estimated cohort incidence rates (expressed per 1,000 person-years) of ischemic heart disease (IHD) and stroke and prevalence of treatment for hypertension and dyslipidemia before and after the IP-MI, as well as cohort rates of MI after the IP-MI.
Results: We identified 132,682 persons with a premature MI in a first-degree relative. Rates of incident IHD in the year before the IP-MI were 0.55 and 0.80 for 35-50 year-old men and women, respectively, 4.26 and 3.71 for 50-65 year-olds, and 7.00 and 6.52 for those >65 years. Corresponding stroke rates were 0.63 and 0.62 for 35-50 year-olds, 3.41 and 2.84 for 50-65 year-olds, and 5.79 and 5.53 for those >65 years. In the year after the IP-MI, IHD and stroke rates increased up to 2-fold. Thereafter, IHD rates, and stroke rates for all but those >65 years, gradually dropped to pre-IP-MI rates; stroke rates in the oldest age group remained elevated >5 years later (men, p=0.003; women, p=0.02). Mean age at MI was 52 and 63 years for cohort men and women, respectively. For persons >50 years, rates of MI were highest 1 year after the IP-MI and then dropped by >65% in subsequent years (p<0.003); MI rates in younger persons were stable over time. Before the IP-MI, 6.5% of men and 12.8% of women were using antihypertensive medication, while 3.0% and 4.2% were using lipid-lowering medication. Initiation of lipid-lowering medication use increased by almost 50% in the year after the IP-MI (p<0.0001 for both sexes), while the prevalence of initiation of

anti-hypertensives rose 20% for men (p=0.002) and remained stable for women (p=0.32).
Conclusions: Our results suggest an intensification of healthcare seeking behaviors immediately after a premature MI in the family; this increased awareness, however, is not sustained long-term. In line with ESC guidelines, a more intensive and systematic clinical focus on screening and follow-up of these first-degree relatives is warranted.

P6070 | BEDSIDE
Comparing hospital performance in treatment and short-term outcome of patients with acute myocardial infarction

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Background: Judging hospitals according to their quality of care is one approach to improve hospital performance. The statistics behind these interhospital comparisons are frequently rather simple and misleading. Our study was aimed at showing that it is feasible to compare the quality of care between departments of cardiology in different hospitals adressing the problems of random variation and differences in patients' mix.
Methods: The BMIR is an ongoing prospective acute myocardial infarction registry. Our analysis was a cross-sectional interhospital comparison of 3571 patients with ST-segment elevation myocardial infarction (STEMI) from 18 hospitals (2010-12), and a longitudinal interhospital comparison for 6312 STEMI patients from 16 hospitals (2007/08, 2009/10, 2011/12). Hospital mortalities were compared by fitting a two-level random effects model with patient characteristics as covariates to the data. The resulting mortalities are Empirical Bayes (EB) estimates adjusted for differences in patient populations between hospitals and with missing data imputated.
Results: In the cross-sectional as well as in the longitudinal comparison there were large interhospital differences in crude hospital mortality rates. After Bayesian shrinkage and adjustment for the differences in patient mix, the range in hospital mortality was reduced in the cross-sectional as well as in the longitudinal comparison with no significant differences between hospitals. Adjusted mortality rates were 8.9% in 2007/08, 8.7% in 2009/10, and 8.5% in 2011/12 (p=0.609).
Conclusion: Our analysis demonstrates that the naïve comparison of hospitals by crude means may be unfair and misleading. A statistical analysis that takes population differences and random effects into account may result in different conclusions and may show stable results for average-size hospitals, if data are pooled over 3 years.

P6071 | BEDSIDE
Association of poor adherence to statins and anti-hypertensive drug regimens with the incidence of cardiovascular events

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Purpose: Nonadherence to treatment hinders the successful management of chronic diseases such as hypertension and hypercholesterolemia. Although studies have suggested that poor adherence would result in a higher incidence of cardiovascular (CV) events, medication adherence differs under different healthcare and social environments and the effects of poor adherence on CV events might differ among populations. Here, we investigated the association between adherence to antihypertensive and/or statin therapy and the incidence of CV events in a general clinical, which is characterized by a fast-aging society, higher incidence of stroke than coronary arterial disease due to hypertension, and relatively high medication adherence.
Methods: We performed a retrospective case-control study using a medical record database that contains medical and prescription data of patients in nationwide hospitals. Among patients treated with both antihypertensive and statin therapy, those who experienced CV events (resulting in death or hospitalization for myocardial infarction [MI], stroke, or other CV diseases) between April 2011 and March 2013 were selected as cases, whereas controls were selected at a 1:4 ratio matched for sex, age, diabetes status, history of CV events, heart failure, and number of prescribed drugs at the index date. Proportion of days covered (PDC), an index of medication adherence, was calculated for 6 months before the index date.
Results: A total of 4,305 patients were studied (861 cases, 3,444 controls; men, 58.7%; mean age, 70.9±10.3 years; diabetes, 74.3%; previous MI, 14.2%). CV events included 73 MI, 533 stroke, 17 MI+stroke, and 231 arterial embolisms and thromboses other than cerebral and coronary, such as venous thromboembolism and pulmonary embolism. Adherence to both antihypertensive and statin therapy was significantly better in the controls than in the cases. PDC in cases and controls was 86.4% and 93.4%, respectively, and the proportions of patients with PDC ≥80% (good "adherers") were 81.0% and 89.4%, respectively. Similar results were obtained with adherence to antihypertensive therapy alone and to statin therapy alone. Comparison between patients with stroke and their matched controls revealed that poor adherence was significantly associated with the incidence of stroke.
Conclusions: Poor adherence to antihypertensive or statin therapy is significantly associated with the incidence of CV events, where medication adherence rates are relatively higher and major CV event types differ from those seen in Western countries.

P6072 | BEDSIDE
Analysis of drugs stored at home by elderly patients with chronic heart failure

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Background: Evidence-based pharmacotherapy improves morbidity and mortality in patients with chronic heart failure (CHF). Medication management and adherence are important components for the effectiveness and safety of the treatment. This study investigated and characterized the drugs stored at home in elderly patients with CHF.
Methods and results: One-hundred-and-one patients with stable CHF age ≥65 years were visited at home and a standardized interview and a thorough assessment of the complete medication were performed. Mean age of the patients was 77.7 years, 53% male, mean NYHA functional class of 2.75 and a Minnesota-Living-with-Heart-Failure score of 59.4 points, indicating poor quality of life. The mean number of different drug packs per patient was 13.1 (range 4-33, mean costs per patient 403€). Cardiovascular drugs accounted for 32% of the packs accounting for 30% of the total costs. On average, 2.4 packs contained medication that was not taken by the patient (18% of the medication, range 0-10, mean costs 61€). Fifty-six percent of the drugs were prescribed by general practitioners, 23% in the hospital, and 7% by medical specialists and 14% were over-the-counter drugs. Sixty-three packages (0.05%) of the drugs at home were expired (mean costs per patient 12€).
Conclusion: On average, elderly patients with CHF have to manage 13 different drug packs at home. New strategies are needed to support medication management at home.

P6073 | BEDSIDE
Changes in the etiology of valvular heart disease

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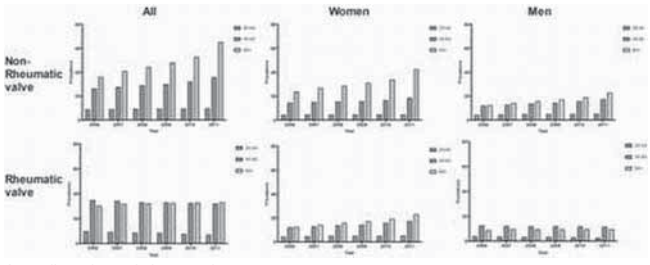
Background: The aim of this study is to assess changes in the causes of valvular heart diseases between 2006 and 2011 in our country.
Methods: Data were collected from the National Health Insurance Service from 2006 through 2011. These data consisted of primary diagnoses related to valvular heart disease diagnosed regardless of other conditions. Valvular heart disease included non-rheumatic mitral valve disorders, non-rheumatic aortic valve disorders, rheumatic mitral valve disorders, and rheumatic aortic valve disorders.
Results: Overall, the age-standardized cumulative prevalence of non-rheumatic valvular heart disease was 70.8 per 100,000 persons in 2006 and 110.3 in 2011. It increased from 42.2 in 2006 to 65.2 in 2011 in women and from 28.4 in 2006 to 45.1 in 2011 in men. In particular, it showed greater increase in the group aged greater than 65 years showed greater increase compared to those in the 20-44 year-old group or the 45-64 year-old group in both genders. The age-standardized cumulative prevalence of rheumatic valve diseases did not change dramatically between 2006 and 2011 year.



Age-adjusted cumulative prevalence.

Conclusions: The overall age-standardized cumulative prevalence of non-rheumatic valvular heart diseases increased between 2006 and 2011, especially in those older than 65 years. These changes should be considered in future designs of cardiovascular healthcare services in rapidly aging countries.

P6074 | SPOTLIGHT

Adherence and uptake of guideline-advocated preventive care in the Australian cohort of the SNAPSHOT Acute Coronary Syndrome Registry

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Purpose: To identify adherence to and uptake of guideline-advocated preventive care during the 18 months after admission for acute coronary syndrome (ACS). Also, to summarise access to medical professionals and secondary prevention programs.
Methods: All patients hospitalised in Australia with ACS were identified between 14-27 May 2012. The Australian death registry, telephone and survey 18 months after discharge was used to determine hospital readmissions, adherence to medications, access to medical professionals and secondary prevention uptake. The EQ5D was collected to assess quality of life.
Results: In total, we followed-up 1485 ACS patients, across 251 hospitals, who survived their index admission. The mean age was 68±13years, median GRACE risk score was 126 (IQR: 104-149), two-thirds were male, 257 (17%) had a discharge diagnosis of ST elevation myocardial infarction, 612 (41%) non-ST elevation myocardial infarction and 616 (42%) unstable angina. During follow-up, 135 (9%) died, 102 (11.2%) experienced a heart attack or stroke, 87 (9.5%) had recurrent angina and 188 (20.6%) underwent coronary revascularisation. Mean number of visits to a family doctor was 11±9 (range 0-40) and to a cardiologist was 2±2 (range 0-23). Of those who survived, 439 withdrew or were un-contactable resulting in 911 survivors completing the follow-up survey. At the time of discharge, 65% of participants were prescribed ≥4 cardio-protective medicines but at 18 months only 273 (30%) were taking ≥4 medicines, including 610 (62%) taking aspirin and 591 (65%) taking a cholesterol-lowering agent. At follow-up, of the 21% who were smokers at baseline 8% had quit with most (44%) doing so spontaneously, one-third (34%) using nicotine replacement therapy and one-quarter using prescription medication. A total of 342 (37%) participants reported having attended cardiac rehabilitation with two-thirds completing the program. Further, 529 (58%) participated in a community exercise program or were regular walkers, 40 (4%) received telephone coaching/counselling and 13 (1.4%) participated in hydrotherapy or another hospital program for chronic disease management. The mean EQ5D health score for the cohort was 74±18 (range 5-100).
Conclusions: Whilst considerable secondary prevention is evident throughout 18 months post ACS, new events and procedures are commonplace and the taking of medicines and management of risk factors can be improved. The systematic delivery of secondary prevention offers one mechanism to a better outcome for all ACS survivors.

P6075 | BEDSIDE

Poor illness perception of symptoms in patients with acute coronary syndrome: a need to improve

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Introduction: The time between onset of symptoms and reperfusion is a critical determinant of prognosis in patients with acute coronary syndrome. Cardiac symptom's interpretation may influence time of hospital admission. We decide to explore illness perception and its predictors among patients with acute coronary syndrome.
Methods: We conducted a cross-sectional study of all consecutive patients admitted at Cardiology department with acute coronary syndrome (ACS) between January 2011 to September 2012. Data was obtained from personal patient registries and telephonic interview asking patients about their perception of the symptoms beginning. The question for all was: "Did you consider the possibility of heart infarction diagnosis when you started chest pain?" Patients without constrictive chest pain and those who had initial symptoms in hospital were excluded.
Results: One hundred and eighty six patients (mean age 63.99±12,34 years old) with ACS were included (12.3% with unstable angina, 38.5% with ST-segment elevation myocardial infarction, 42.8% with no ST-segment elevation and 6.4% with undetermined ECG location). The majority (62.6%) of patients didn't have perception of ACS, until the doctor information. Among those who had perception, 82.6% were men and 58% had previous ischemic coronary disease diagnosis. Patients with arterial hypertension and dyslipidemia had superior illness perception (p=0.05; p=0,02; respectively). Only 27.5% of patients with ST- segment elevation myocardial infarction had perception of cardiac disease. No association was found between ACS perception and age, academic degree and residence (rural vs urban). Among patients with ACS, only 29% decided to seek a hospital within the first thirty minutes of symptoms. Of those, the illness perception was present in 42%.
Conclusions: The illness perception of patient with acute coronary syndrome needs to be improved, independently of socio-demographic factors. An educational program for the general population, focusing in the alert signs for ACS may be necessary to improve hospital admission time and treatment in this setting.

P6076 | BEDSIDE

Trends in acute myocardial infarction incidence and mortality a long term follow-up of a primary prevention program in Sweden

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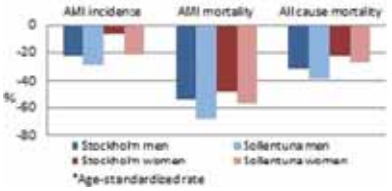
Background: In 1988 a cardiovascular prevention program, combining an individual and population based strategy, was launched in primary health care in Sollentuna municipality (Sollentuna).
Aims: To study time trends in incidence and mortality of acute myocardial infarction (AMI), and all-cause mortality during two decades after implementation of a cardiovascular prevention program within Sollentuna municipality in Stockholm County, Sweden.
Methods: AMI incidence and AMI- and all-cause mortality were obtained for the population of Stockholm County minus Sollentuna municipality (Stockholm) and Sollentuna during the study period using national registries.
Incidence and mortality were calculated by calendar years and gender using the mean population as denominator. Differences between the groups were studied as the interaction effect in a multiple analysis of variance with year and group as independent variables. The average population was 1 795 504 in Stockholm and 56 589 in Sollentuna during 1987-2010.
Results: During the period 370 295 deaths (48% men) and 135 958 AMI cases (58% men) were observed in Stockholm and 8504 deaths (50% men) and 3 207 AMI cases (60% men) in Sollentuna. AMI death was registered in 50 365 cases (55% men) in Stockholm and 1 011 (58% men) in Sollentuna. The AMI incidence declined more in women from Sollentuna compared to women from Stockholm (on average -22% vs. -7%; p for difference in slope <0.05) (Fig. 1).

Figure 1. The relative change (%) of AMI incidence and mortality, and all-cause mortality in men and women from Stockholm, and Sollentuna between 1987-1989 and 2005-10 *



Conclusion: The decreased acute myocardial infarction incidence and mortality, and all-cause mortality may indicate a positive effect of cardiovascular prevention and treatment in general. Acute myocardial infarction incidence declined significantly more in women from Sollentuna compared to women from Stockholm.

P6077 | BEDSIDE

Comparing quality of care with administrative or registry data? QS-AMI Project for assessing quality of hospital care of patients with acute myocardial infarction in Berlin

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Background: Assessing quality of health care on the basis of administrative data is becoming a common approach in German health care policy despite studies missing that have evaluated the validity of using these data for the purpose of quality assurance. Therefore we have initiated the QS-AMI project in which data routinely collected for reimbursement purposes by one of the biggest german sickness funds (AOK Nordost) are compared to data collected by a clinical quality registry (Berlin Myocardial Infarction Registry - BMIR) for patients with acute myocardial infarction (AMI).
Methods: All AMI patients treated in 20 Berlin hospital between 2009-11 from the AOK and BMIR data sets were included and both pseudonymized data sets were analysed separately first. Using key variables (patients' sex, age, and day and time of hospital admission) data were linked and those patients considered being the same patient in both data sets were identified. The level of agreement between the variables collected in both data sets for patients identified as being the same was calculated using the cappa coefficient (CC).
Results: 7738 AMI patients were enclosed from AOK and 9297 from BMIR. In a first descriptive analysis both data sets showed many differences: AOK patients were older, more often women, received PCI less often und died more often in the hospital. Through linkage we were able to identify 2558 patients, considered to be identical in AOK and BHIR. This was about 80% of the assumed possible overlap with the following results: AOK and BMIR data are comparable for coding of STEMI vs. NSTEMI (CC: 0,824), for aspects important for reimbursement i.e. procedures like PCI (CC: 0,860), or relevant secondary diagnoses, i.e. Diabetes (CC: 0,814), or for hard outcome parameters, i.e. hospital mortality (CC: 0,915).

AOK and BMIR data are not comparable for coding of risk factors or secondary diagnoses not important for reimbursement, i.e. smoking (CC: 0,394). AOK data have only a limited capacity to summarize patients history, i.e. previous AMI (CC: 0,004). AOK data cannot differentiate between "present on admission" and "during hospital stay", which leads to more patients being diagnosed with i.e. CHF in the AOK data set compared to the BMIR (CC: 0,212).
Conclusion: The AOK data set can give an overview of existing structures, processes (i.e. PCI), and hospital mortality. The BMIR can provide additional data on risk factors, secondary diagnoses and patients' history necessary for adjusting for hospital mortality.

P6078 | SPOTLIGHT
Teachers' knowledge and attitudes related to rheumatic heart disease

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Purpose: Rheumatic heart disease (RHD) is a major public health problem in Africa affecting 1-5% of school-aged children. Community and school involvement is increasingly recognized to be an essential component of national strategies to control RHD, but very little is known about teachers' knowledge and attitudes about the disease. As part of a public-private partnership to combat RHD in Zambia, school-based screening of up to 10,000 school children will be conducted in Lusaka for the first time using portable echocardiography. In preparation, we sought to characterize teachers' knowledge of RHD, explore their willingness to participate in RHD screening programs, and assess their general interest in participating in RHD advocacy efforts.
Methods: A workshop was conducted for primary and secondary school teachers in February 2014. The curriculum was developed from educational materials produced by the World Health Organization and the World Heart Federation, and included a focus group session and written attitude survey. Participants also completed an 8-item multiple-choice questionnaire before and after the course to evaluate basic knowledge about RHD. Mean test scores were compared using paired Wilcoxon signed rank sum testing (SOFA software, version 1.3.4).
Results: Fifty-three teachers from more than 45 schools participated. Most were female and all but 3 had been teachers for at least 5 years. Approximately half of the teachers also served as their school's health officer. Only 55% had ever heard of RHD before the workshop, and 24% reported that they had known a student with RHD. Forty-nine percent of teachers were unaware that RHD is caused by bacterial infection of the throat and few (less than 25%) knew that children with RHD require regular antibiotics to prevent progression of their heart disease. Pre-post knowledge scores improved from 3.8/8 (SD 0.9) to 5.9/8 (SD 1.2; $p<0.001$). In the focus group discussion, teachers were overwhelmingly eager to help facilitate RHD screening programs at their schools. They also expressed interest in learning more about how to prevent and treat RHD in order to help keep their students healthy.
Conclusion: Teachers' baseline awareness of RHD is poor and few report first-hand exposure to students with RHD despite the high prevalence of the disease in Africa. Notwithstanding, teachers were eager to learn about RHD and demonstrated significantly improved knowledge after the workshop. Teachers appear poised to be vital partners in school-based screening programs and may also play important roles in long-term efforts to control RHD.

P6079 | BEDSIDE
Electrocardiographic abnormalities associated with increased risk of development and progression of chronic kidney disease

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Introduction: There is a close relationship between cardiovascular disease and chronic kidney disease (CKD). Although we have identified that atrial fibrillation is associated with increased risk of renal dysfunction, the association of common electrocardiographic (ECG) abnormalities with CKD is unknown.
Methods: This prospective observational cohort study was based upon an annual health check-up program in Japan. We studied the effects of ECG abnormalities on development and progression of CKD in 227,342 subjects (72,908 men; age, 61.0±11.7 years).
Results: 1) ECG risk factors for CKD development. During a follow up of 5.9±2.3 years, 14,507 subjects (6.5%) without baseline CKD newly developed proteinuria. In the multivariate models, left bundle branch block (HR, 1.55; 95% CI, 1.16-2.06), left ventricular hypertrophy (HR 1.63; 95% CI, 1.41-1.83), ST-segment abnormality (HR 1.44; 95% CI, 1.36-1.52), and presence of premature beats (HR 1.37; 95% CI, 1.20-1.56) were associated with development of proteinuria. During a follow-up, 8,517 subjects newly developed renal dysfunction. The multivariate models revealed that PR prolongation (HR, 1.25; 95% CI, 1.102-1.53), left ventricular hypertrophy (HR, 1.36; 95% CI, 1.14-1.62), ST-segment abnormality (HR 1.20; 95% CI 1.18-1.29), and premature beats (HR 1.45; 95% CI, 1.24-1.70) were associated with development of renal dysfunction (eGFR <60 mL/min/1.73m^2). To exclude the effects of cardiovascular diseases, the multivariate analyses were repeated after exclusion of subjects who had hypertension and/or heart disease. Left ventricular hypertrophy, ST-segment abnormality, and premature beats remained associated with development of renal dysfunction and proteinuria.
2) ECG risk factors for CKD progression. Among 4,240 subjects with eGFR <60 mL/min/1.73m^2 at baseline, in 850 subjects (20%) had further decrease of renal function ($\geq$10 mL/min/1.73m^2 decline of eGFR) during a follow-up. In the multivariate models, left ventricular hypertrophy (HR 1.92; 95% CI, 1.15-3.20) and premature beats (HR 1.63; 95% CI, 1.04-2.54) were associated with progression of CKD.
Conclusion: Various ECG abnormalities increased the risk of development and progression of CKD.

CARDIOMETABOLIC DISORDERS

P6081 | BEDSIDE
Zonulin, a potential biomarker of metabolic inflammation and pulmonary endothelial permeability, in an AICD cohort

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Background: In obesity and metabolic syndrome, disturbed intestinal permeability and low-grade chronic systemic inflammation appear to act in a vicious circle called metabolic inflammation. Zonulin, a tight junctions modulator and key regulator of intestinal permeability, has been shown to be up-regulated in individuals with type-1 diabetes and to play a role in gut-related dysfunctional auto-immunity. In addition, there are some preliminary reports indicating a possible association between zonulin and metabolic inflammation or type-2 diabetes as well. Moreover, zonulin is implicated in the regulation of general endothelial/epithelial permeability, and its association with increased pulmonary permeability has been demonstrated in animal experiments.
Methods: This study aimed at investigating plasma zonulin and its dependence on various clinical and biochemical factors in 225 patients carrying automatic implantable cardioverters/defibrillators (AICD), with 75% of them suffering from systolic heart failure, 69% from coronary artery disease (CAD), and 27% from type-2 diabetes (T2D).
Results: Univariate linear regression analysis showed that zonulin levels were associated with plasma creatinine, plasma nitrotyrosine, severity of CAD, left ventricular ejection fraction, and NYHA functional class, but not with high-sensitivity C-reactive protein (hsCRP), body mass index, weight, height, sex, or age. After multiple linear regression analysis, the negative association with creatinine ($p=0.006$) and the positive one with NYHA class ($p=0,013$) remained significant. In the subgroup of individuals with T2D, multiple regression revealed a significant positive affection of zonulin by hsCRP only ($p=0.025$).
Conclusions: These findings may support reports on zonulin's involvement in the phenomenon of metabolic inflammation in T2D patients. The association of zonulin with NYHA may reflect its newly established role in altering endothelial/pulmonary permeability in heart failure. The robust negative correlation with creatinine is unexpected and needs further clarification in experimental and clinical studies.

P6082 | BEDSIDE
Relationships between epicardial fatty tissue and gestational diabetes mellitus

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Purpose: We aimed to investigate the relation between EFT thickness that is measured with transthoracic echocardiography (TTE) and GDM.
Methods: 91 pregnant women in third trimester (46 pregnant women with GDM and 45 pregnant women without complications as control) were included in the current cross-sectional study. The diagnosis of GDM was done with abnormal 2-hour oral glucose tolerance test (OGTT) by using the criteria of World Health Organization. TTE were performed in all subjects.

Table 1. Clinical characteristics and transthoracic echocardiography measurements of study patients

Variables	GDM group	Control group	P value
Age (year)	29.9±5.6	30.2±4.3	0.73
Body mass index (kg/m^2)	28.8±4.5	25.6±3.7	<0.01
Serum glucose (mg/dL)	98.5±14.1	89.2±9.5	<0.01
Post prandial serum glucose (mg/dL)	187.9±37.2	132.4±9.2	<0.01
Left ventricular ejection fraction (%)	64.3±5.2	63.0±4.4	0.20
E wave	0.76±0.2	0.78±0.17	0.68
A wave	0.61±0.1	0.57±0.1	<0.01
Deceleration time	191.8±47.5	181.1±26.1	0.19
isovolumetric relaxation time	93.2±37.8	68.1±17.6	<0.01
E/A	1.2±0.3	1.3±0.3	0.02
E/E'	6.6±1.9	6.1±2.2	0.19
Epicardial fat thickness (mm)	6.9±2.4	5.7±1.8	0.01

Results: Body mass index (BMI), serum glucose and postprandial blood glucose were significantly higher in GDM group compared to the control group ($p<0.01$). No significant difference was observed between groups in terms of heart rate, systolic and diastolic blood pressure measurements, Hb, creatinine and lipid parameters. In GDM group, A wave, E/A, and IVRT parameters were found to be significantly different when compared with control group. EFT measurement was significantly increased in GDM group (p=0.01). EFT was correlated with Post prandial glucose, waist circumference, BMI, age and heart rate, in the gestational diabetic patients (Table 1).
Conclusion: In the present study we found that the EFT measured with TTE is high in patients with GDM. These results demonstrate that EFT thickness measured with TTE is an important determinant for development of GDM.

P6083 | BEDSIDE
Disease duration and cardiovascular perspective in type I diabetes mellitus

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Purpose: Innovative simultaneous assessment of micro- and macrovascular abnormalities in type I diabetes mellitus (DM) may be essential to understand the increased cardiovascular mortality. We sought to assess cardiac microcirculatory abnormalities, endothelial dysfunction, atherosclerosis and the relationship with disease duration (DD).
Methods: One hundred and twenty asymptomatic type I DM patients with DD varying from 5 to 52 years were included. All patients underwent Doppler of the carotid arteries and a CT-scan at two different levels for coronary calcium score (CACS, Agatston score, GE 64-slice) and abdominal visceral fat measurement. A complete 2D, Doppler and tissue-Doppler imaging rest echocardiography was followed by a Dobutamine stress myocardial contrast perfusion echocardiography (Philips iE-33 using echocontrast Sonovue) to assess contractile and perfusion abnormalities at baseline and peak stress. Fasting blood samples were taken for extensive laboratory analysis.
Results: Fifty eight percent (70/120) were men with a mean age of 46.7±12.3 years, BMI 25.9±4.2 kg/m^2, HbA1c 7.64±0.92% and DD of 25.3±10.3 years. At baseline 57% had diastolic dysfunction with a LVEF of 69±8%, CACS range 0 – 3405 and visceral fat range 52 -140 cm^2. Analysis of tertiles (<20 years, 20-30 years, >30 years) by DD showed increasing abnormalities in diastolic function, extent of inducible perfusion defects (PD) and functional reserve with increased CACS and carotid plaques ($p<0.003$ for all). Functional reserve showed significant negative correlation with age, DD, BMI, visceral fat, fibrinogen, extent of inducible PD, total and percentile coronary calcification ($p<0.05$ for all), while extent of myocardial PD showed significant positive correlation with all except fibrinogen ($p<0.05$ for all). Regression analysis showed a significant relationship between DD and functional reserve ($R^2=0.26$, p=0.003) after correction for age, BMI, visceral fat, CACS, fibrinogen and HbA1c. Furthermore, Poisson model fitting showed a significant association with DD and extent of inducible PD ($p<0.03$).
Conclusions: Our data shows progressive cardiovascular abnormalities with increasing DD regardless of glycaemia control in type I DM. After correction for age and CACS, DD remains significantly associated with extent of inducible myocardial PD and functional reserve.

P6084 | BEDSIDE
Screening for diabetes in chronic systolic heart failure: How do the the new HbA1c criteria perform compared to oral glucose tolerance testing?

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Purpose: To compare the prevalence and long-term prognostic impact of newly detected diabetes diagnosed either by Hemoglobin-A1c (HbA1c) or by oral glucose tolerance testing (OGTT) in chronic systolic heart failure (CHF) patients.
Methods: We assessed glycemic status in 254 outpatients (age 69±11 years, 67% male) with CHF, a left ventricular ejection fraction (LVEF) ≤45%, and without known diabetes. Newly detected diabetes was defined as an HbA1c level ≥6.5% or by OGTT if either fasting or post-load glucose concentrations were ≥7.0 mmol/L and ≥11.1 mmol/L, respectively. Information on age, sex, ischemic heart disease, N-terminal pronatriuretic B-type peptide concentrations, estimated glomerular filtration rate, hemoglobin, BMI, LVEF and dosages of loop-diuretics was collected at baseline and adjusted for in survival models. Median follow-up time was 4.8 years (interquartile range 3.8-6.1 years) during which time 77 (30%) patients died.
Results: Of 254 patients newly detected diabetes was diagnosed by HbA1c in 35 (14%) whereas the proportion diagnosed by OGTT was 51 (20%). Sixty-nine (27%) had newly detected diabetes by either criteria, but only 17 (7%) by both (Fig. 1). Newly diagnosed diabetes was independently associated with increased all-cause mortality compared to patients without diabetes when detected by HbA1c (adjusted HR: 2.4, 95% CI: 1.2-4.9, P=0.02) and trend-wise when detected by OGTT (adjusted HR: 1.8, 95% CI 0.9-3.3, P=0.08).

Figure 1

Conclusions: HbA1c and OGTT detect different populations with diabetes among CHF patients. Thus, these methods can be considered complementary in the assessment of risk related to glucose metabolism, since newly detected diabetes is frequent by either criterion and seems associated with an approximate 2-fold increase in long-term mortality.

P6085 | BEDSIDE
Effects of obesity and weight loss on diastolic function, functional capacity, chronotropism and blood pressure in apparently healthy individuals

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Effects of obesity on cardiovascular system in healthy individuals have not been sufficiently studied in a multimodal, integrated way.
Methods: 359 apparently healthy patients, 40.8% obese, 42.5±7.4 years old (24-65), 84.7% men, were studied by echocardiogram, exercise test on treadmill, and routine blood test. Obese patients were offered a program of diet, exercise, and monthly control, with 24h-blood pressure monitoring, echocardiogram, blood sample and exercise test at inclusion and after 6 months.
Results: Obese patients exhibited a worse diastolic function (E/A 1.25±0.3 vs 1.48±0.4 m/s. E' by tissue-doppler 13.4±3.8 vs 16.9±11.2 cm/s; p=0.017), achieved a worse functional capacity (11.6±2.2 vs 14.8±2.4 MET) with a higher maximal SBP (173±14 vs 168±12 mmHg), showed a higher basal heart rate (79±13 vs 70±14 bpm), blood pressure (SBP/DBP 127±10/81±6 vs 120±10/76±7 mmHg), and a worse chronotropic response (heart rate reserve 91 vs 101 bpm).
22.9% of obese patients completed a 6-month program based on diet and exercice achieving weight loss (BMI 29,7±3,8 vs 33,7±3.4), improvement in diastolic function (E' by DTI 16.1±4.3 vs 10.9±3.5 cm/s; p=0.021), functional capacity (14.5±2.6 vs 11.8±2 METs on exercise test), risk profile (2.5±1.5 vs 4.2±3.3% by DORICA score; p=0.039), analytic parameters (Glycemia 88.9±9 vs 95.3±17; p=0.037.Insuline 9.8±5.7 vs 13.8±7.9 mcUI/mL; p=0.01. Total cholesterol 186±42 vs 203±38 mg (dL; p=0.05. LDLc 116.8±36 vs 130.5±30 mg/dL; p=0.006), and a reduction in 24-h-BP-monitoring: mean SBP 117.24±8.2 vs 127.14±14.8; p=0.002, mean DBP 73.8±7.2 vs 79.9±9.3 ($p<0.0001$ for all except when referred).
Conclusions: Obesity decreases diastolic function, functional capacity and chronotropic response, increases blood pressure and heart rate. Weight loss and exercise improve these items, risk score, analytic parameters, and blood pressure measured by 24h-BP-monitoring.

P6086 | BEDSIDE
Carotid plaque burden is related to impaired glucose metabolism among patients with acute coronary syndromes

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Background: Type 2 diabetes (DM2) and impaired glucose tolerance (IGT) are established risk factors for atherosclerosis. The aim of this study was to evaluate the atherosclerotic plaque burden in the carotid arteries of patients with acute coronary syndromes and relate it to the presence of newly diagnosed DM2, IGT, or normal glucose metabolism (NGM).
Methods: Ninety-eight ACS patients (male 77%, age 63 years) with no previous diagnosis of DM2 were consecutively included in the study. Measurements of glucose metabolism were made before hospital discharge and repeated 3 months later. Atherosclerotic plaques in bilateral bifurcations of the common carotid and internal carotid arteries were evaluated with ultrasound examination and patients classified as having none, minimal, moderate or severe atherosclerotic plaques.
Result: Atherosclerotic plaques were found in 97%, 98% and 100% of patients with NGM, IGT and DM2, respectively. The prevalence of moderate or severe carotid plaques was 47%, 56% and 91% in patients with NGM, IGT and DM2, respectively. Carotid artery plaque burden was significantly related to impaired

Table 1

	NGM	IGT	DM2
None	1 (3%)	1 (2%)	0 (0%)
Minimal	16 (50%)	23 (42%)	1 (9%)
Moderate	12 (38%)	30 (54%)	6 (55%)
Severe	3 (9%)	1 (2%)	4 (36%)

glucose metabolism (p=0.006).between in patients diagnosed with NGM, IGT or DM2.
Conclusion: Carotid atherosclerotic plaque is found in nearly all patients with ACS. The severity of plaque burden is directly related to impaired glucose metabolism. Newly diagnosed DM2 among ACS patients indicates a high likelihood of moderate or severe carotid plaque burden.

P6087 | BEDSIDE
Increased left ventricular mass reduces left ventricular diastolic function more in healthy subjects with elevated fasting glucose levels: a cross-sectional study

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Purpose: The ratio of the peak early mitral inflow velocity (E) to early diastolic mitral annulus velocity (e') provides a good approximation of left ventricular filling pressure with increasing values corresponding to increasing filling pressure. The objective of this study was to examine whether worsening of glucometabolic status is associated with increasing values of E/e' ratio independently of higher left ventricular mass index (LVMI) in middle-aged or older apparently healthy subjects.
Methods: We examined cross-sectional associations between the E/e' ratio (using the average e' obtained from the septal and lateral parts of the mitral annulus), LVMI, and fasting plasma glucose (FPG) categorized as normal fasting glucose (NFG: FPG≤6.0mmol/L), impaired fasting glucose (IFG: FPG 6.1-6.9mmol/L) and diabetes mellitus (DM: FPG≥7.0mmol/L), in 498 men and 214 women aged 56-79 years without overt cardiovascular disease who received no cardiovascular, antidiabetic or lipid lowering drugs and had a preserved left ventricular ejection fraction (≥50%). Correlations were assessed using Pearson product moment correlation, and the associations were further evaluated using multiple linear regression analysis.
Results: In separate age and sex-adjusted models, FPG category was significantly associated with both LVMI (beta=2.04[95% confidence interval (CI), 0.07-4.00]; p=0.04) and E/e' ratio (beta=0.39[95% CI, 0.13-0.66]; p=0.004). E/e' ratio and LVMI were likewise significantly correlated (r=0.22; p<0.001), and the strength of the correlation increased with worsening glucometabolic status (NFG: r=0.081, p=0.1; IFG: r=0.29, p<0.001; DM: r=0.36, p<0.001) due to a significant interaction between LVMI and FPG category (p=0.002). After adjusting for traditional cardiovascular risk factors, E/e' ratio remained significantly associated with LVMI (beta=0.025[95% CI, 0.015-0.035]; p<0.001), independently of age (beta=0.22[95% CI, 0.19-0.26]; p<0.001), sex (beta=1.58[95% CI, 1.08-2.08]; p<0.001), systolic blood pressure (beta=0.012[95% CI, 0.002-0.022]; p=0.02), and HDL cholesterol (beta=-0.85[95% CI, -1.37 to -0.32]; p=0.002).
Conclusion: E/e' ratio was positively associated with LVMI independently of traditional cardiovascular risk factors, and the strength of the association increased with worsening glucometabolic status, possibly due to myocardial glycosylation.

P6088 | BEDSIDE
Cardiovascular events and mortality in immigrants and long-term residents with diabetes: are all immigrants healthier?

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Purpose: Cardiovascular events are responsible for half of all deaths among diabetics. While immigrants have been found to be healthier on arrival compared to long-term residents, this difference disappears with time in a host country. The objective of this study was to examine whether the healthy immigrant advantage leads to lower cardiovascular risk among individuals with diabetes and if so, whether this effect persists over time and among all immigrants.
Methods: We examined the impact of immigration on the risk of cardiovascular events (acute myocardial infarction, unstable angina, congestive heart failure, transient ischemic attack, stroke) or all-cause mortality from March 31st, 2005 until February 29th, 2012 using linked population-based databases from our region. Adults (≥20 yrs) with diabetes who immigrated to our region from 1985-2002 and long-term residents matched on age, gender and location of residence were included in our cohort. The risk of cardiovascular events or mortality was also stratified by socioeconomic status, neighborhood of settlement, immigration class, level of education, marital status, region of birth and time since immigration.
Results: 87,707 immigrants and 87,707 long-term residents with diabetes were included in our cohort. Immigrants had shorter duration of diabetes (diabetes >10 yrs 19% vs 27%, P<.001), less use of health care (35% vs 41% for high & very high utilization, P<.001), and were more likely to be from the lowest income quintile (34% vs 21%, P<.001) when compared to long-term residents. There was a lower adjusted rate of cardiovascular events or all-cause mortality among immigrants (HR=0.76, 95%CI=0.74-0.78) which persisted beyond 10 years regardless of age, gender, socioeconomic status, neighborhood of settlement, and use of health care (HR=0.75, 95%CI=0.73-0.77). However, a healthy immigrant effect was not found among immigrants from all regions of birth nor among refugees (HR=0.93, 95%CI=0.81-1.08), those with no education (HR=1.08, 95%CI=0.84-1.40), or who were unmarried (HR= 0.80, 95%CI=1.03) until 10 years or more after landing.
Conclusion: Immigrants with diabetes have lower risk of cardiovascular events and all-cause mortality when compared to long-term residents extending beyond 10 years following time of immigration. Not all immigrants benefit from this health advantage initially however. Further research is needed to better understand reasons for variations in cardiovascular events and mortality among immigrants at higher risk within the first 10 years of arrival.

P6089 | BEDSIDE
Metabolic syndrome is a risk factor for contrast-induced nephropathy after percutaneous coronary intervention

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Purpose: Contrast-induced nephropathy (CIN) is the third most common cause of acute renal failure. It is also associated with increased morbidity and mortality rates, prolonged hospitalization and potential need for dialysis. Screening patients who are vulnerable to development of CIN is essential to reduce this complication. We aimed to investigate the effect of metabolic syndrome (MetS) on the development of CIN in patients who underwent non-urgent percutaneous coronary intervention (PCI).
Methods: A total of 599 patients who underwent PCI were divided into two groups: Three hundred and thirteen MetS patients and 286 age and gender adjusted controls were enrolled. Serum creatinine levels were measured before and 48 h after angiography. CIN was defined as an increase in serum creatinine of ≥25% or ≥0.5 mg/dl above the baseline value 48 hours after angiography.
Results: Baseline clinical and demographic characteristics were similar between groups (table). Serum creatinine levels were increased in both groups (from 0.96±0.46 to 1.15±0.65 mg/dl in MetS, p=0.03 and from 0.98±0.27 to 1.05±0.50 mg/dl in control, p=0.07). However significantly higher levels of serum creatinine were observed among patients with MetS than control patients 48 h after PCI (1.15+0.65 vs 1.05+0.50 respectively, p=0.04). CIN occured in 9.3% (29 of 313) of the MetS group and 4.9% (14 of 286) of the control group (p=0.04).

Table 1. Baseline characteristics of groups

Characteristics	Patients with MetS (n=313)	Patients without MetS (n=286)	P
Age (mean ± SD)	61±9	62±10	0.38
Male gender, n (%)	222 (71)	197 (69)	0.84
Active smoking, n (%)	47 (15)	51 (18)	0.48
Previous myocardial infarction, n (%)	104 (33)	92 (32)	0.78
ACEi/ARB use, n (%)	217 (69)	189 (66)	0.40
Volume of contrast agent (ml ±SD)	168.2±91.3	157.7±77.0	0.36
Baseline serum creatinine (mg/dl ±SD)	0.96±0.46	0.98±0.27	0.42

Conclusion: MetS is associated with higher incidence of CIN in patients who undergo PCI. We recommend to check the MetS status in all patients before PCI.

P6090 | BEDSIDE
Epicardial adipose tissue is related to left ventricular viability in patients with chronically occluded left anterior descending coronary artery

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Purpose: Mechanisms underlying the reported lower mortality in obese patients with coronary artery disease ("obesity paradox") remains unclear. Epicardial adipose tissue (EAT), especially in obesity, is metabolically active, capable of secreting various vasoactive cytokines and located in direct proximity to coronary vasculature. It can be hypothesized that EAT impacts collateral circulation development. This study sought to determine relationships between EAT and myocardial viability in relation to BMI in patients with chronically occluded left anterior descending coronary artery (LAD).
Methods: Consecutive patients with chronically occluded LAD as assessed with angiography or computed tomography and myocardial viability assessed with cardiac MRI between 2008 and 2013 were retrospectively included. Viability was assessed on late gadolinium enhancement MRI images and expressed as the per-

centage of viable segments in 17-segment model of left ventricular myocardium. EAT quantity was obtained in standardized fashion from MRI images by manually tracing EAT area in 4 chamber view and expressed in cm^2. Traditional cardiovascular risk factors were collected by telephone and medical records review.
Results: The studied cohort included 62 patients (mean age 63.2±10.0yrs, 11.3% were women). Mean BMI was 27.1±3.7kg/m^2, mean EAT area 16.7±4.9 cm^2, mean viability 75±22%. No correlation was found between EAT area and myocardial viability in the entire cohort (r=-0.14, p=0.26). There was a significant correlation between EAT and myocardial viability in patients with BMI in the 3rd tertile (BMI >28.4kg/m^2, r=-0.57, p=0.006). This correlation remained significant after adjustment for age, sex, BMI, and traditional cardiovascular risk factors (p=0.049). There was no correlation between EAT area and viability in the 1st (BMI <24.2 kg/m^2, r=-0.15, p=0.61) or 2nd (r= -0.04, p=0.84) tertiles. BMI determined presence of the relationship between EAT and viability in interaction analysis (p=0.03).
Conclusions: Greater amount of epicardial adipose tissue is related to greater myocardial viability in the settings of chronically occluded LAD in patients with higher BMI.

P6091 | BEDSIDE
Association of sleep apnea related nocturnal hypoxia with oxidized ldl in obese participants of a weight loss program

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Purpose: Central obesity and sleep apnea (SA) are both associated with a higher risk of cardiovascular disease and mortality. Moreover oxidized LDL (oxLDL) is known to play an important role in pathogenesis of arteriosclerosis. The aim of the study was to test whether central obesity and SA-related hypoxia are associated with increased plasma oxLDL.
Methods: Sixty-four obese participants (mean age 42±11 years, 44% male and mean body-mass index 41±8 kg/m^2) of a structured 1-year weight-loss program were studied. All participants were examined with a home-based 2-channel-screening device for SA (measuring nasal flow and oximetry). An apnea-hypopnea index (AHI) of ≥15/h indicates moderate to severe SA. Waist-to-hip ratio was used as a surrogate for the degree of central obesity.
Results: Moderate to severe SA was present in 28% of participants of the program. Increased waist to hip ratio and reduced mean SaO were significantly related (Betacoefficient, β [95% confidence interval]: -7.38 [-12.39, -2.38], p=0.005). While there was no significant association between BMI as well as the AHI and oxLDL (β=0.33, [-0.381, 1.04], p=0.356; β=0.24,[-0.08, 0.56], p=0.140, respectively), there were significant correlations between waist-to-hip ratio (β=75.755 [25.647, 125.864], p=0.004), LDL (β=0.45 [0.29, 0.60], p<0.001) and mean SaO2 (β=-4.51 [-6.77, -2.25], p<0.001) with oxLDL. In the multiple regression analysis SaO2mean (β=-3.28 [-5.24, -1.32], p=0.002) and LDL (β=0.37 [0.22, 0.52], p<0.001) remained significantly associated with oxLDL, whereas the waist-to-hip ratio was not (β=22.174 [-20.736, 65.084], p=0.304).
Conclusion: SA is common in obese participants of weight loss programs. SA-related nocturnal hypoxia is an independent risk factor of an increased plasma oxLDL. Whether treatment of SA may lower plasma oxLDL merits further investigation.

P6092 | BEDSIDE
Influence of overweight on echocardiographic parameters

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Purpose: Influence of body size on echocardiographic parameters has led to the need to index them by the body surface area and to establish a normal reference values for clinical practice according to body size, age and gender. Whether the presence of overweight (Body mass index ≥0.25) influence echocardiographic parameters has not been previously addressed. We aim to report the influence of Body mass index (BMI) on echocardiographic parameters in a contemporary cohort of healthy patients.
Methods: NORRE study is a multi-centre study involving accredited echocardiography laboratories of the European Association of Cardiovascular Imaging (EACVI) studying echocardiographic parameters according to recommended echocardiographic approaches in a large cohort of healthy population (n=726; 45.8±13.3 years; 43.6% of male). All 2D echocardiographic parameters were indexed by the body surface area and compared according to the group of BMI ≥25 (n=261) or <25 (n=465).
Results: LV mass index was significantly increased in patients with overweight (73.3±18.3 vs. 68.0±16.7; p<0.001) and in the subgroup of women with BMI ≥25 (70.2±16.6 vs. 64.4±16.1; p=0.002). There were no significant differences in the left ventricle (LV) volumes index according to the BMI group (LV end-diastolic volume 50.9±12.2 vs. 51.7±11.0 ml/m^2; p=0.412), neither there were in the right ventricle (RV) end-diastolic area (8.9±2.0 vs. 9.1±2.0 cm^2/m^2; p=0.601) or in the LA volume index (29.1±7.2 vs. 28.3±6.5; p=0.275). Male patients with overweight presented a smaller RV end-diastolic area (9.1±2.1 vs. 9.6±2.1 cm^2/m^2; p=0.016) and right atrium volume (22.6±6.0 vs. 25.3±7.6; p=0.21).
Conclusion: Overweight (BMI ≥0.25) does not influence the size of left and right ventricle, and also not the LA size. Differences in RA volume and RV end-diastolic area in men might be related to the monoplane measurement of these parameters and to the higher weight in this subgroup of patients.

METABOLISM AND HEART

P6094 | BEDSIDE
Cardiovascular safety of dapagliflozin in type 2 diabetes mellitus (T2DM) patients with various degrees of cardiovascular risk

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Purpose: Patients with T2DM are at increased risk of cardiovascular (CV) disease. Dapagliflozin (DAPA), an SGLT2 inhibitor, lowers blood glucose by increasing urinary glucose excretion and also reduces weight and blood pressure. In a pre-specified meta-analysis of DAPA vs control (CTRL; placebo or active) the incidence rates per 100 years of exposure for the primary composite end point of CV death, myocardial infarction (MI), stroke or hospitalisation for unstable angina were 1.62 for DAPA vs 2.06 for CTRL, HR 0.79 [95% CI 0.58, 1.07]. We further characterise the effects in subgroups of patients with various degrees of CV disease with a focus on major adverse CV events (MACE; composite end point of CV death, MI or stroke).
Methods: In total 9339 patients with T2DM from 21 clinical phase 2b and 3 studies were included (5936 patients received DAPA and 3403 received CTRL). One third, 3214 patients, had prior CV disease. CV events were systematically identified from adverse events reports and independently adjudicated in a blinded manner. In total 176 primary events and 134 MACE events were observed, of which 128 and 95, respectively, occurred in patients with prior CV disease.
Results: DAPA showed a favourable point estimate for MACE regardless of the number of risk factors for CV disease beyond diabetes (≥0 to ≥6 of: history of CV disease, hypertension, dyslipidemia, smoking, family history, advanced age, or renal impairment). The results for MACE were similar in patients with and without prior CV disease (HR 0.80 [95% CI 0.53, 1.22] and HR 0.65 [95% CI 0.34, 1.24] respectively). A favourable or neutral estimated HR for MACE was observed in patients with different types of prior CV disease: coronary artery HR 0.94 [95% CI 0.59, 1.49] (based on 75 events); cerebrovascular HR 0.89 [95% CI 0.46, 1.71] (37 events); peripheral vascular HR 0.37 [95% CI 0.15, 0.88] (27 events); and CHF HR 1.04 [95% 0.39, 2.83] (20 events). In patients with prior CV disease, DAPA showed a favourable point estimate for MACE irrespective of the number of different types of prior CV disease (0 to 4 of: coronary artery, cerebrovascular, peripheral vascular or CHF). Hypoglycaemia as a putative risk factor did not appear to have an effect; the HR was favourable regardless of whether or not hypoglycaemia was experienced.
Conclusions: Consistent results for MACE were observed in patients with various degrees of CV risk. The results suggest that DAPA is not associated with increased risk of CV events and raise the hypothesis of benefit, which will be tested prospectively in the ongoing DECLARE study.

P6095 | BEDSIDE
Metformine and Contrast-Induced Nephropathy in Diabetic patients treated with Primary Percutaneous Coronary Intervention for ST segment elevation myocardial infarction STEMI: a multicentre study

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Background: Contrast-induced nephropathy (CIN) is a frequent complication in patients undergoing percutaneous coronary intervention (PCI), associated with increased mortality. The impact of metformin, which has potential interactions with renal function, on CIN remains to be investigated.
Aim: To analyze the association between chronic metformin treatment and the development of CIN after primary PCI for ST segment elevation myocardial infarction (STEMI).
Methods: 372 patients with diabetes mellitus (DM) treated with PCI <24H in 2 coronary care units (Paris-Bichat and Dijon Hospital, France) were included. Serum creatinine (Cr) was measured before and 48H after PCI. CIN was defined as an increase in Cr of 44μmol/L (0.5 mg/dL) or 25% over baseline after PCI. Since PCI was urgent, metformin could not be withheld prior to PCI but was usually stopped after PCI.
Results: Mean age was 66±11 y, and 25% were women. 64% had hypertension, 56% had DM duration >5 year, and 26% had prior coronary artery disease. Metformin and sulfonylurea were the most frequently used antidiabetic chronic treatments (40% for both), and 27% were on insulin therapy. The other antidiabetic medications, including glinide, glitazone, and acarbose were rarely used (3%, 2%, and 5%, respectively). Mean baseline and post PCI Cr levels were 102±52 and 122±81 μmol/L. Rate of CIN was similar in patients with or without metformin (21 vs 20%, respectively, p=0.87). Logistic regression for the risk

of CIN taking into account classical risk factors showed no impact of chronic metformin therapy, even in stratified analysis in patients with chronic kidney disease. Hospital mortality was similar between groups (7 vs 6%, respectively, p=0.69). Moreover, no case of lactic acidosis was reported during the hospital stay.
Conclusion: In this multicentre study reflecting current clinical practice, metformin treatment prior to primary PCI had no significant impact on CIN. Larger studies are needed to confirm these findings.

P6096 | BEDSIDE
Genetic susceptibility of type 2 diabetes in our population

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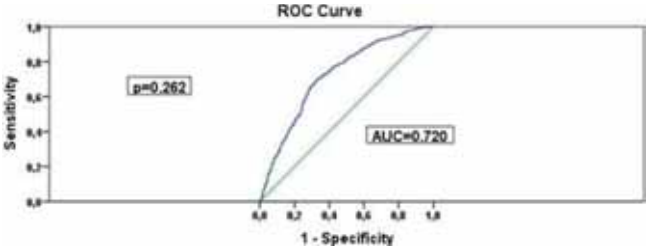
The prevalence of type 2 Diabetes Mellitus (T2D) has increased sharply around the world and the actual estimation suggests that this trend will continue to rise over the next decade. Recently, new GWAS in this field allowed finding new biological pathways and potential therapeutic and preventive approaches.
Aims: To assess whether a group of genetic variants, previously associated to T2D risk by GWAS, can predict T2D susceptibility.
Methods: A case-control study was performed with 1405 participants: 621 diabetics selected according to the IDF criteria and 784 controls, adjusted for age and gender. Eight genetic variants associated with T2D by GWAS were genotyped. Quantitative data were assessed by Student's t-test and Mann-Whitney, while qualitative data were assessed by chi-square test. The power of association was expressed by OR and 95% CI. A p-value <0.05 was considered significant. A logistic regression determined which variants were associated with T2D. A ROC curve estimated the AUC and Hosmer-Lemeshow tested the model calibration.
Results: The genetic variants that showed statistical significance as risk factors of T2D were: ADIPOQ GG (OR=1.72; p=0.025) and TCF7L2 TT (OR=1.48I; p=0.011). After logistic regression, the ADIPOQ GG and TCF7L2 TT showed an increased risk of T2D (OR 1.81; p=0.027 and 1.59; p=0.010, respectively) as well as BMI, hypertension, smoking, dyslipidemia and sedentary life. The AUC indicated a good accuracy of the model (72%) and the Hosmer-Lemeshow test estimated an adequate calibration (p=0.262).



T2D susceptibility (ROC curve).

Conclusion: In our population, ADIPOQ GG and TCF7L2 TT were found to affect the susceptibility to T2D. Individuals carrying these variants should be advised to adopt a healthy lifestyle in order to alter the genetic predisposition, especially in younger age groups.

P6097 | BEDSIDE
Long term effects of therapy with DPP-4 Inhibitors on fitness, cardiovascular function and mortality: a cohort study in elder population

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Purpose: The impact of DPP-4 Inhibitors on long-term major clinical outcomes in type 2 diabetes remains unknown. We examined cardiac fitness, incidence of heart failure, major cardiovascular events and cardiovascular mortality associated with all available DPP-4 Inhibitors compared with usual therapy with metformin in elder subjects.
Methods: Elder patients (range 65-90 ys), in therapy with DPP-4 Inhibitors, metformin or combined therapy between 2007 and 2013, were followed for up to 6 years (median 4.9 years). Fitness was assessed with use of some tests, such as Short Physical Performance Battery (SPPB) and 6 minutes Walking Test (6MWT), using ANOVA test. Diagnosis of Heart failure, according to ESC Guidelines 2012, was evaluated using Chi square test and relative risk. The composite of myocardial infarction (MI), stroke, and cardiovascular mortality associated with individual DPP-4 Inh was investigated in patients by multivariable Cox proportional-hazard analyses including propensity analyses.
Results: A total of 1374 subjects were included. Compared with metformin, results for the composite endpoint in patients in therapy with sitagliptin (hazard ratios and 95% confidence intervals): 1.05 (0.91-1.18), saxagliptin: 1.09 (0.93-1.23) and vildagliptin: 1.02 (0.90-1.28), were not statistically different from metformin. Incidence of Heart Failure was significantly lower in patients in therapy with DPP-4 Inhibitors [Sitagliptin RR 0.71 (0.51-0.96); Saxagliptin RR 0.76 (0.35-0.91); Vildagliptin RR 0.72 (0.35-0.95)]. Besides, elder subjects treated with DPP-4 Inhibitors showed a significant difference in fitness compared to metformin group [Sitagliptin p value 0.02 (0.001-0.91); Saxagliptin 0.04 (0.01-0.97); Vildagliptin 0.03 (0.01-0.93)].
Conclusions: Monotherapy with the most used DPP-4 Inhibitors, including sitagliptin, vildagliptin and saxagliptin, seems to be associated with lower risk of heart failure and improvement in fitness. No differences were found in major cardiovascular events and cardiovascular mortality compared with metformin and combined therapy.

P6098 | BEDSIDE
Physical activity moderates the effect of lipid levels on diabetes incidence: 10-year (2002-2012) follow-up of the ATTICA study

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Aim: The aim of this work was to elucidate the association between lipids profile and incidence of diabetes mellitus, as well as to investigate the potential moderating effect of physical activity in this relationship.
Methods: During 2001-2, 1514 men and 1528 women (>18 years) without any clinical evidence of cardiovascular disease (CVD) at the baseline examination, living in Athens greater area, Greece, were enrolled in the ATTICA study. In 2011-12, the 10-year follow-up was performed. Several demographic, lifestyle, clinical and biochemical characteristics of the participants, as well as physical activity status and dietary habits, were evaluated, in relation to the development of diabetes as defined according to WHO-ICD-10 criteria (fasting blood glucose>125 mg/dL or the use of antidiabetic medication). Glucose, total cholesterol (TC), oxidized LDL cholesterol, HDL-cholesterol and triglycerides were recorded, using fasting blood samples. The LDL/HDL and TC/HDL cholesterol ratios were calculated as well. Participants were classified based on their physical activity level, using IPAQ questionnaire, in two categories: active or sedentary.
Results: The 10-year incidence of diabetes was 11.6 per 100 men and 11.2 per 100 women. Data analysis revealed that high total cholesterol (>200mg) was found to increase 47% the 10-risk of diabetes (95%CI 1.04, 2.09). Similarly, TC/HDL ratio increased diabetes incidence (Relative Risk 1.47, 95%CI 1.04, 2.09). However, after splitting the sample based on physical activity status, hypercholesterolemia and TC/HDL ratio were associated with diabetes incidence, only among sedentary participants (Relative Risk 1.62, 95%CI 1.04, 2.54 and 1.24, 95%CI 1.05, 2.45, respectively), whereas for physically active participants the results were not significant.
Conclusions: This work underlines the deleterious effect of high lipid levels on the development of diabetes mellitus; however, this association was found to be moderated by physical activity level, as only physically inactive participants were affected.

P6099 | BEDSIDE
Outcome of sulfonylurea and insulin vs. incretin-based treatment in type 2 diabetes patients uncontrolled on prior metformin mono therapy - results of DiaRegis

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Background: Metformin is the first line treatment of type-2 diabetes (T2D). The impact of different treatment escalation strategies for metformin mono-therapy-failure on glucose control and morbidity has not been investigated in the real life setting.
Methods: DiaRegis is a multicenter registry of 3,810 patients with T2D. For the present analysis we selected patients who were on metformin mono-therapy at baseline, and in whom either incretin-based drugs (Incretin), Sulfonylureas (SU), or Insulin were added.
Results: At baseline 2,064 patients received metformin mono-therapy. Incretin (DPP-4 I or GLP-1 A) was added in 38.0% of patients (n=783), SU in 15.7% (n=324) and insulin in 12.9% (n=266). For 81.7% of these patients, a 2-year follow-up was available of which 65.4% retained the originally chosen treatment strategy (incretin n=421; SU n=154; insulin n=151). Compared to Incretin, SU resulted in a higher HbA1c reduction vs. baseline (-0.6±1.4% vs. -0.5±1.0%; p=0.039). Insulin resulted in a larger reduction of HbA1c (-0.9±2.0% vs. -0.5±1.0%; p=0.003), and fasting plasma glucose (-24±70 mg/dl vs. -19±42 mg/dl; p=0.001), but was associated with an increase in bodyweight (0.8±9.0 kg vs. -1.5±5.0 kg; p=0.028) after 2-years compared to Incretin. Hypoglycaemia rates were higher in patients with Insulin (OR 8.35; 95%CI 4.84-14.4) and SU (OR 2.70; 95%CI 1.48-4.92) compared to Incretin. While there was no difference in event rates between Incretin and SU, treatment with Insulin was associated with higher rates of death (OR 4.65; 95%CI 1.68-12.9), major cardiac and cerebrovas-

	Metf./Incr (n=421)	Metf./SU (n=154)	OR (95%CI)* vs. Metf./Incr	Insulin (n=151)	OR (95%CI)* vs. Metf./Incr
Death	1.7%	3.2%	2.11 (0.65–6.87)	7.3%	4.65 (1.68–12.9)
Combined endpoints within 24 months					
Death / MI / Stroke	2.6%	5.8%	2.31 (0.93–5.78)	8.0%	3.08 (1.27–7.48)
MIC	7.7%	6.0%	0.87 (0.40–1.90)	20.7%	3.84 (2.13–6.90)

cular events (MACCE: OR 3.08; 95%CI 1.27-7.48) and incident micro-vascular disease (MIC: OR 3.84; 95%CI 2.13-6.90).
Conclusions: Outpatients with T2D not controlled on metformin mono-therapy showed different incident macro- and micro-vascular complication rates in clinical practice dependent on the treatment strategy chosen, with highest death-, MACCE and MIC-rates for those on insulin treatment as compared to patients with incretin-based treatment.

P6100 | BEDSIDE
Microalbuminuria (MAU) is closely related with brachial-ankle pulse wave velocity (baPWV) and baPWV can predict MAU in Type 2 diabetic patients

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Purpose: Microalbuminuria (MAU) is an important and sensitive marker of subclinical atherosclerosis and pulse wave velocity (PWV) is known to be an indicator of arterial stiffness. However little is known about the direct association between MAU and PWV in type 2 diabetic patients. The aim of this study was to examine whether MAU is associated with brachial-ankle PWV (baPWV) and also baPWV predict MAU in type 2 diabetic patients.
Methods: 424 type 2 diabetic patients were enrolled and we excluded patients with renal insufficiency (serum creatinine >1.5 mg/dl) or macroalbuminuria (≥200 μg/min). Urinary albumin concentration was determined by the short-time urine collection method and MAU was defined as 20~200 μg/min. baPWV was measured with using an automated device (VP-1000, Colin, Co, Ltd, Komaki, Japan). We divided the patients into two groups according to the amount of albuminuria as a normoalbuminuria group [<20 μg/min (n=331)] and MAU group [20-200 μg/min (n=93)].
Results: baPWV was significantly higher in MAU group compared with normoalbuminuria group (1,932±175 cm/sec, 1,435±184 cm/sec, P<0.001). When all study subjects were divided according to the amount of albuminuria, baPWV was increased by the amount of the albuminuria (1 Quartile = 1,242±135 cm/sec, 2 Quartile = 1,429±76 cm/sec, 3 Quartile = 1,592±84 cm/sec, 4 Quartile = 1,910±175cm/sec, Kruskal-Wallis test P<0.001). the amount of albuminuria in all study subjects was significantly correlated with baPWV (r=0.791, P<0.001) and even though in normoalbuminuria group, amount of albuminuria was also closely related with baPWV (r=0.863, P<0.001). In multiple regression model among all study subjects, log (baPWV) was significantly correlated with log (MAU) (β=0.132, R2=0.904). In this study, the best cutoff value of the baPWV to predict MAU 20 μg /min was 1,700 cm/sec (95.7% sensitivity, 89.7% specificity, and area under the curve (AUC) =0.976).
Conclusions: The amount of MAU is a significantly correlated with baPWV and more than 1,700 cm/sec baPWV could be predict MAU in type 2 diabetic patients.

P6101 | BEDSIDE
Impact of hyperuricemia on development of new-onset diabetes mellitus in Asian population: five-year clinical outcomes

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Background: Hyperuricemia is a well-known risk factor for diabetes mellitus (DM) and other cardiovascular diseases, but the relationship between hyperuricemia and the development of new-onset DM is not clear. We evaluated the impact of hyperuricemia on the development of new-onset DM based on 5-year cumulative clinical outcomes in Asian patients.
Methods: A total of 3,274 patients who did not have DM were enrolled. New-onset DM was defined as having a fasting blood glucose ≥126mg/dL or HbA1c ≥6.5%. Hyperuricemia was defined as uric acid ≥7.0 mg/dL. Baseline characteristics between the hyperuricemia and control groups were matched with propensity score matching (PSM, C-statistics=0.731). 5-year cumulative incidence of new-onset DM was compared between the two groups.

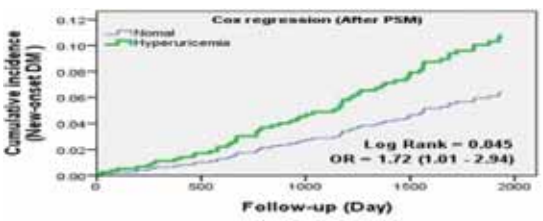

Figure. Impact of hyperuricemia on new-onset DM following PSM analysis

Results: At baseline, patients in the hyperuricemia group showed a higher prevalence of male gender, hypertension and dyslipidemia. The hyperuricemia group had higher levels of basal insulin, HOMA-IR, triglyceride and lower levels of HDL-C. Development of new-onset DM was higher in the hyperuricemia group (13.5% vs. 7.9%, p<0.001). After PSM, baseline characteristics were well balanced (C-statics=0.731). After adjustment with cox-regression analysis, hyperuricemia remained to be a independent predictor of new-onset DM (OR 1.72, 95% CI 1.01-2.94, p=0.045, figure).
Conclusions: Hyperuricemia was shown to be an independent predictor of new-onset DM. Therefore it may be suggested that uric acid levels should be included in the prediction of DM and patients with hyperuricemia may benefit from measures to reduce the uric acid.

P6102 | BEDSIDE
Leptin serum levels are independently determined by obesity and by the presence of the metabolic syndrome

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Purpose: Obesity is a major risk factor for the metabolic syndrome (MetS), but some obese individuals do not have the MetS while others have the MetS but are non-obese. The single and joint associations of the adipokine leptin with obesity and the MetS have not yet been investigated and are addressed in the present study.
Methods: We measured leptin in four groups of patients: subjects who were non-obese and did not have the MetS (n=196), non-obese patients with the MetS (n=149), obese subjects who did not have the MetS (n=13) and obese patients with the MetS (n=77). Obesity was defined as a BMI ≥30kg/m^2; presence of the MetS was defined according to the current harmonized consensus definition.
Results: Compared to serum leptin in non-obese subjects who did not have the MetS (6.71±7.83 ng/ ml), leptin was significantly higher in non-obese subjects with the MetS (9.29±7.53 ng/ml; p<0.001), as well as in obese subjects without (11.15±9.75 ng/ml; p=0.016) or obese patients with the MetS (15.92±11.61 ng/ml; p<0.001), in whom leptin trendend (p=0.127) to be higher than in obese patients without the MetS and was significantly (p<0.001) higher than in non-obese patients with the MetS. Analysis of covariance showed that both obesity and the MetS significantly and independently predicted serum leptin, with obesity being the stronger predictor (F=17.016; p<0.001) than presence of the MetS (F=7.60; p=0.006).
Conclusions: Obesity and presence of the MetS are independent determinants of serum leptin, but obesity explains a larger amount of serum leptin variation than the presence of the MetS.

P6103 | BEDSIDE
Indexes of obesity and cardiac remodeling: is body mass index enough?

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Purpose: Body Mass Index (BMI) has been widely employed as a reliable anthropometric index of overweight and obesity. However, evidence in favour of a pivotal role of abdominal obesity in cardiovascular disease has emerged. Waist to height ratio (WHtR), a new index which takes into account fat distribution, has been proposed as an alternative tool for patients' risk stratification. Little information, however, is available about the respective power of BMI and WHtR to discriminate patients with echocardiographic parameters indicative of unfavourable cardiac remodeling.
Methods: We evaluated 813 consecutive adult asymptomatic patients, referred for risk factors evaluation and treatment. All patients underwent a complete echocardiographic evaluation; patients with ejection fraction <50% or valve disease more than mild were excluded. Receiver Operating Characteristic (ROC) curves were employed in order to evaluate the power of BMI and WHtR to discriminate patients with cardiac remodeling. The dichotomisation of echocardiographic parameters was made according to American Society of Echocardiography cut-off values.
Results: The study population consisted of 813 patients (males 44.2%, mean age 57.9±12.2 years; females 55.8%, mean age 58.0±13.5 years). The prevalence of obesity and hypertension was respectively 59.5% and 77.7%. WHtR showed

Obesity indexes and cardiac remodeling. Receiver operating characteristic (ROC) curves

	Body mass index AUC	Waist to height ratio AUC
Left atrial dilation	0.672 (p<0,001)	0.697 (p<0,001)
Left ventricular diastolic dilation	0.656 (p<0,001)	0.623 (p<0,001)
Left ventricular hypertrophy	0.679 (p<0,001)	0.725 (p<0.001)
Relative wall thickness >0.42	0.561 (p=0.025)	0.594 (p<0.001)
Left ventricular diastolic dysfunction	0.535 (p=0.103)	0.544 (p=0.040)

AUC, Area under the curve.

higher areas under the curve (AUC) in identifying left atrial dilation, left ventricular hypertrophy, relative wall thickness >0.42 and diastolic dysfunction, while BMI had a higher AUC in identifying left ventricular dilation.
Conclusions: In a population with high prevalence of obesity and hypertension, WHtR seems to provide additional information to BMI and should therefore be incorporated in the routine clinical evaluation of these patients.

THE COST OF HEART DISEASE: ECONOMIC AND PSYCHOSOCIAL

P6105 | BEDSIDE
Comparison of costs between transradial and transfemoral percutaneous coronary intervention: data from one large single center in China

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Purpose: To evaluate the costs and complications of transradial percutaneous coronary intervention (TRI) and transfemoral percutaneous coronary intervention (TFI) from one large single center in China.
Methods: The study was a retrospective inpatient cohort analysis using medical data of patients undergoing percutaneous coronary intervention (PCI) in 2010 in our hospital. The primary outcome was the cost of PCI during hospitalization. Cost was obtained from our hospital's cost accounting system. Independent costs of TRI and transfemoral intervention (TFI) were identified using propensity-scoring matching methods.The secondary outcome included the in-hospital mortality and the length of stay.
Results: In 6068 PCI procedures performed from 1st January to 31st December in 2010 in our hospital, except for those patients with chronic thrombotic obstruction (CTO), cardiac stroke and no expense invoice, 5539 cases were analyzed. 4888 (88.2%) cases were in TRI access and the others were in TFI approach (n=651, 11.8%). There were 508 TRI cases matched with 508 TFI cases. The total costs of TRI were lower than TFI group (¥58971±25189 vs. ¥68558±29114). TRI access was associated with a cost saving of ¥9587 (95% confidenceinterval [CI]: ¥6236 to ¥12939; p<0.001), of which ¥4834 (95% CI: ¥2189 to ¥7479; p<0.001) were procedural savings and ¥4753 (95% CI: ¥3187 to ¥6319, p<0.001) were post-procedural savings. Compared to TFI group, the lengths of stay in TRI group was shorter (3.3-day vs. 4.2-day; p<0.001), and the rate of bleeding events was lower (0.8% vs. 2.6%; p=0.024). However, there were no significant differences in the inhospital mortality (TRI vs. TFI 0.0% vs. 0.0%), myocardial infarction (TRI vs. TFI 2.0% vs. 2.2%; p=0.825), stroke (TRI vs. TFI 0.0% vs. 0.6%; p=0.249) and revascularization (TRI vs. TFI 0.2% vs. 0.6%; p=0.624) between the groups.
Conclusions: Compared to TFI approach, TRI was associated with lower total hospitalization costs, lower incidence of bleeding events and shorter length of hospital stay.

P6106 | SPOTLIGHT
The prevalence of acute myocardial infarction during Greek financial crisis in the Cardiology Department of a greek central Hospital

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Introduction and purpose: Cardiovascular morbidity and mortality tend to increase during periods of crisis, such as war, social depression or natural disasters. The financial crisis that Greece is experiencing during the last years bears major social implications, such as unemployment and poor quality of life. The purpose of the present study was to investigate the prevalence of acute myocardial infarction (AMI) during the period of financial crisis.
Methods: Two separate time periods were studied retrospectively regarding the prevalence of AMI in the Cardiology Department of a greek central Hospital. The period from 1.1.2003 until 31.12.2007 was considered the "pre-crisis period", while the period 1.1.2008 until 31.8.12 was defined as "crisis period".
Results: The results are shown in Table 1.
Conclusions: The above results indicate an increase in the number of admissions due to AMI in both sexes during the "crisis period" compared to the "pre-crisis period". This increase was statistically significant in women (P<0.001) but not in men. The prevalence of AMI was increased in patients younger than 45 years old during the "crisis period", but the increase was statistically significant again only for women (P<0,01). The prevalence of AMI was also increased in males without social insurance (P=0.04).

Table 1

	Pre crisis period		Crisis period	
	Male	Female	Male	Female
Number of admissions	1903	1517	2015	1845
Number of AMI	444 (23.3%)*	221 (14.6%)*	569 (28.2%)*	412 (22.3%)*
<45 years old	66 (14.9%)†	39 (17.6%)†	89 (15.6%)†	94 (22.8%)†
Patients without social insurance	61 (13.7%)†	22 (10%)†	133 (23.4%)†	55 (13.3%)†
Patients without risk factors for coronary disease	31 (7.0%)†	15 (6.7%)†	42 (7.4%)†	29 (7%)†

*Number and percentage of acute myocardial infarction cases on the total of admissions† number and percentage on the total of acute myocardial infarction cases.

P6107 | BEDSIDE
Economic burden and resource utilisation in secondary care due to hospitalisation for atrial fibrillation

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Introduction: Due to an ageing population, incidence and prevalence of Atrial fibrillation (AF) is predicted to increase,with a rise in the use of health care resources. Only limited data are available on the impact of hospitalisations due to AF on secondary care in the UK.
Methods: Consecutive patients with AF, admitted between Apr 2012 - Jan 2013 identified. Records of 100 patients with a primary diagnosis (PD Grp) and 416 with a secondary diagnosis (SD Grp) analysed with regard to: demographics, length of stay, underlying diagnoses, management strategy, investigations, medication, CHADSVASc Score and anticoagulation therapy.
Results:
Total AF admissions: 4602 [PD Grp: 536 (11.6%), SD Grp: 4066 (88.4%). PD Grp: AF type: Paroxysmal 56%, Persistent 27%, Permanent 15%. Treatment strategy: rate control: 64%, rhythm control: 20% and rate followed by rhythm control: 16%. Commonest drug for rate and rate followed by rhythm control: bisoprolol. Rhythm control: commonest drug: amiodarone; commonest intervention: DCCV. SD Grp: Top 4 reasons for admission: chest infections, COPD, congestive heart failure and ACS. Mean non pay cost (NHS reference costs 2012/13) per patient for PD Grp: £2053 (median: 1208, range: 604-10,872). Costs for the SD Grp substantially higher.
Conclusions: Large number of patients admitted to secondary care with AF. Patients in the SD Grp were significantly older and had a longer length of stay, hence consuming more resources. Need for anticoagulation was high, was suboptimal and and did not differ between the two groups. Suprisingly, amiodarone was the popular choice for rhythm control in elderly patients as compared to drugs with lesser known side effects. Respiratory and cardiac conditions were the most common precipitants in the SD Grp. The economic burden due to AF hospitalisation was substantial and is predicted to increase in future.

P6108 | SPOTLIGHT
Cost impact of left atrial appendage occlusion to prevent stroke in patients with nonvalvular atrial fibrillation

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Purpose: Recent evidence supports left atrial appendage (LAA) occlusion as a cost-effective alternative to warfarin. However these findings, based on clinical trial populations, may not be generalisable to clinical practice. The cost-impact of a real world experience of LAA occlusion compared with warfarin, dabigatran, rivaroxaban, apixaban and no therapy in patients with nonvalvular atrial fibrillation (AF) is unknown.
Methods: Cost minimisation analysis using a cost impact model was used to systematically assess the costs of Watchman device implantation over a 10 year time horizon to determine the costs of LAA occlusion in relation to all other treatment strategies in patients with nonvalvular AF at risk of stroke, with and without contraindications to anticoagulation. Complications and subsequent stroke rates were determined from our experience of 85 implants in 84 patients (Age 70.8±9.7, CHA2DS2-VASc 4.6±1.7, HAS-BLED 3.9±1.2). Watchman implantation and complication costs were obtained from UK NHS 2014 tariffs, while those for stroke and bleeding were sourced from peer-reviewed literature. Overall cost-impact of Watchman device implantation was quantified as time to achieve cost parity with other strategies and cost saved over 10 years.
Results: Cost parity was achieved between 3.5 (vs Rivaroxaban) to 5.4 (vs Apixaban) years. Cost saving over 10 years ranged between 42.8% against PROTECT

Abstract P6107 – Table 1

Parameter	Whole cohort (n=466)	Primary diagnosis (n=100)	Secondary diagnosis (n=416)	P value Primary vs Secondary
Mean age±SD, median, range (years)	78.7±11.2, 81, 38–98	71.8±15.8, 76, 37–94	79.6±10.2, 81, 38–98	<0.001
Male (%)	48.3	44	49.5	ns
Length of stay: mean±SD, median, range (days)	7.9±6.9, 6, 1–39	3.4±3.5, 2, 1–18	8.3±7.0, 6. 1–39	<0.001
Mean CHA2DS2Vasc score	–	2.9	2.9	ns
% of patients who should have been anticoagulated	–	86	91	ns
% of patients anticoagulated	–	48	49.5	ns

Abstract P6108 – Table 1. Event rates and patient level costs

	Ischaemic stroke (rate per 100 patient years)	Haemorrhagic stroke rate (rate per 100 patient years)	Major bleeding (rate per 100 patient years)	Systemic embolism (rate per 100 patient years)	Severe disability secondary to stroke (rate per 100 patient years)	Mortality (rate per 100 patient years)	Mean cumulative cost per patient (10 years)	Cost saving†	Time to achieve cost parity†
Watchman (Royal Brompton prospective data)	1.45	0.92	2.69	0	1.71	19.52	£7,337.23	N/A	N/A
Watchman (PROTECT AF study data)	12.67	1.71	14.12	2.38	5.07	28.2	£12,831.03	42.8%	N/A
Warfarin	16.51	10.29	27.08	N/A	19.27	46.82	£14,452.74	49.2%	5.1 YRS
Apixaban	16.17	1.81	15.97	0.61	14.17	33.31	£13,213.05	44.5%	5.4 YRS
Dabigatran 150mg	14.62	0.85	23.08	0.7	13.78	33.41	£15,305.13	52.1%	4.5 YRS
Dabigatran 110mg	17.51	0.99	20.21	0	16.91	33.78	£17,083.22	57.1%	4.2 YRS
Rivaroxaban	22.08	4.12	32.47	0	30.38	21.67	£24,346.84	70.0%	3.5 YRS
No therapy	42.43	0.85	28.85	N/A	21.43	47.31	£20,761.68	64.7%	3.9 YRS

†Watchman Royal Brompton data vs other strategies.

AF data (£7337.23 vs £12831.03) and 70.0% against Rivaroxaban (£7337.23 vs £24,346.84).

Conclusion: LAA occlusion in real world practice can substantially reduce costs relative to all other treatment strategies, including clinical trial data of LAA occlusion, over a relatively short time horizon for patients at risk with nonvalvular AF.

P6109 | BEDSIDE
Factors predictive of change in sexual activity after cardiac diagnosis

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Purpose: Sexual activity after cardiac diagnosis often declines, although little is known about changes over time. This study examined predictive factors for change in sexual activity before and after cardiac diagnosis.

Methods: Cardiac patients (N=192), through self-report survey, reported frequency of sexual activity before their cardiac problem and the past 2 months. Participants were categorized into 3 groups: sex as frequently as before (n=68), sex less often (n=93), and no sex prior to diagnosis nor presently (n=31, control group). The survey included demographic questions and a Sexual Concerns Inventory (SCI, rated "never" to "frequently", 3 subscales), with 2 items on ED combined for patient/male partner's ED, for 11 total items (R=0-33). Statistical analysis: chi-square, ANOVA, logistic regression.

Results: Bivariate testing showed those of younger age had sex as frequently as before (M=63 years, SD 12.4), compared to controls (M=70 yrs, SD 12.5). Those single, not working, with "enough"/"not enough" finances, and current/former smokers (59%; 31% never smokers) were less likely to have sex as frequently as before. Control group and those having sex as frequently as before, SCI scores were similar (M=6 and 6.6), while those having sex less often had more concerns (M=10.8, SD 7.28, $p<.05$). For logistic regression, the outcome variable was coded as having sex less often (0) and as frequently as before (1); the control group was removed to clearly determine predictors of less frequent sex. Those with higher SCI scores and having ever smoked had sex less frequently, while those with higher education and still working were more likely to have sex as before diagnosis (Table).

Predictors of change in sexual activity

Predictors	Parameter estimate	Std. Error	Odds Ratio
(constant)	–0.957	0.787	0.384
SCI score	–0.092**	0.030	0.912
Education	0.409*	0.166	1.505
Employment status	1.073**	0.381	2.925
Ever smoked	–0.974*	0.385	0.378

Nagelkerke R2=0.292, ***Regression analysis: *$p<0.05$, **$p<0.01$, ***$p<0.001$. N=161; sex less often (0), same frequency (1).

Conclusions: Findings highlight the importance of addressing sexual concerns and identifying cardiac patients who most need support in maintaining sexual function over time.

P6110 | BEDSIDE
First medical contact in STEMI patients; utilization of healthcare advice via telephone in the acute phase - a survey report from the SymTime study group

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Introduction: In our country the general public has the additional opportunity to phone a joint services number (1177) when having need for in-depth healthcare advice. This service is staffed by advisement nurses 24/7, to answer questions, determine the need for further care, and provide advice and/or recommend other healthcare agencies. It is unknown into what extent individuals utilize 1177 instead of 112 when falling ill in STEMI. We hypothesised that STEMI patients turn to ambulance services as the first medical contact in the acute phase.

Methods: SymTime is a Swedish multicentre observational study where STEMI patients admitted to the CCU fill in a validated Swedish questionnaire within 24h from admission. The questionnaire measures e.g. symptoms and pre-hospital actions in ACS patients.

Results: 109 women and 334 men were included (mean age 71 and 65 years, respectively). In total, 224 patients (50%) turned to 112 as their first medical contact; 21% (n=93) utilised 1177, while 16% (n=66) chose to contact their general primary healthcare centre, and 13% (n=60) went directly to the emergency department. STEMI patients turning to 1177 were predominating women (28% vs. 19%, $p<.05$), without any history of MI (23% vs. 9%, $p<.05$), and experiencing pain in throat/neck (33% vs. 18%, $p<.01$). Those utilising 112 had more frequently a history of MI (74% vs. 47%, $p<.001$), heart failure (83% vs. 50%, $p<.05$), atrial fibrillation (77% vs. 49%, $p<.01$), experiencing chest pain (53% vs. 34%, $p<.01$), radiating pain in their arms (57% vs. 42%, $p<.01$), and cold sweat (55% vs. 44%, $p<.05$).

Conclusion: Only half of the STEMI patients utilise the ambulance service when falling ill. Every fifth patient contacts advisement nurses by phone as their first medical contact, jeopardising a rapid reperfusion.

P6111 | BEDSIDE
Symptoms in MI in patients with and without diabetes: a survey report from the SymTime study group

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Introduction: Previous studies on myocardial infarctions (MI) symptoms report inconclusive results whether there are differences between patients with and without diabetes. Atypical symptoms can contribute to a less probability of prompt care seeking and a correct diagnosis. We hypothesised that chest pain is equally common in patients with and without diabetes in a MI population. We further hypothesised that patients with diabetes have more other atypical symptoms.

Methods: SymTime is a Swedish multicentre observational study where patients with MI, admitted to the CCU fill in a validated Swedish questionnaire within 24h from admission. The questionnaire measures how patients with MI describe their symptoms and actions in the pre-hospital phase.

Results: 94 patients with diabetes and 600 without diabetes were included. Unadjusted data showed that chest pain was more common in patients without diabetes, 88 vs 82%, $p<0.05$. Shoulder pain was more common in patients with diabetes (Table). Regarding atypical symptoms such as tiredness, dyspnea, cold sweat, vertigo, diaphoresis and anxiety, only tiredness were more common in patients with diabetes, 45 vs 31%, $p<0.05$. Cold sweat was more common among patients without diabetes. 54 vs 43%, $p<0.05$.

Symptom locations in MI patients

Symptom location	Total n (%)	Diabetes n (%)	No diabetes n (%)	P-value
Chest	612 (88)	77 (82)	535 (89)	0.038
Throat	143 (21)	25 (27)	118 (20)	NS
Jaw/teeth	80 (12)	15 (16)	65 (11)	NS
Back	117 (17)	19 (20)	98 (16)	NS
Stomach	58 (8)	10 (11)	48 (8)	NS
Shoulders	144 (21)	34 (36)	110 (18)	<0.001
Arms/hands	380 (55)	51 (54)	329 (55)	NS

Conclusion: Chest pain was the most common symptom in both groups. Chest pain and cold sweat was more common in patients without diabetes, pain in shoulders and tiredness were more common in patients with diabetes. Other symptoms were equally common in both groups.

P6112 | BEDSIDE

Sexual dimorphism in marital and socioeconomic differences regarding the risk factors, symptomatology and management of patients with coronary artery disease in Poland - the results of RECENT trial

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Background: In Western Europe there are proven relationships between socioeconomic status (SES), marital status (MS) and the risk factors, prevalence, treatment and outcomes among patients with coronary artery disease (CAD). All of this data from Poland is scant.
Methods: We analyzed the data of 2593 patients with stable CAD from RECENT study. SES is influenced by many factors, of which education, constitutes a most commonly used SES measure in epidemiological studies, hence was applied in this analysis. As regards the reported level of educational attainment, patients were divided into three groups (primary educated, secondary educated and highly educated). According to MS, patients were split up into two groups - participants declaring marriage formed married population (MP), while all the others were incorporated into single population (SP).
Results: When groups according to MS were analyzed no differences in prevalence of risk factors and applied treatment between sexes were found. Married subjects generally more often: smoke ($p<0.01$), are overweight ($p<0.01$) and give a history of hyperlipidemia ($p<0.01$) or myocardial infarction ($p<0.01$). On the other hand invasive (PCI $p<0.01$; CABG $p<0.01$) as well as evidence-based pharmacological treatment ($p<0.01$) is applied more often in that group then in single individuals. The control of CAD symptoms is associated with sex - the usage of long lasting nitrates ($p<0.05$) and CCS class ($p<0.01$) are higher in single women, but not in men.
Considering SES, there is stronger relationship in the prevalence of risk factors in female than in male subjects. Low education in women is associated with overweight ($p<0.01$), higher systolic ($p=0.04$) and diastolic ($p=0.03$) diastolic blood pressure and worse heart rate control ($p<0.01$). However, smoking is more frequent in highly educated women ($p<0.01$), than in those with lower education. Invasive treatment (PCI $p=0.03$; CABG $p<0.01$) and statins ($p<0.01$) are implemented more often in subjects holding higher education, regardless of sex. SES is a good predictor of symptoms control - highly educated patients of both sexes are in lower CCS class ($p<0.01$) and report chest pain ($p<0.01$) as well as usage of nitroglycerin ($p<0.01$) less frequently than the others.
Conclusion: MS and SES differentiate Polish CAD patients in terms of risk factors, applied treatment and symptoms control. Hence those characteristics should be considered as indicators of patients being in need of an intensified medical attention.

P6113 | BEDSIDE

Impact of percutaneous coronary intervention on twelve-month chronic total occlusion outcomes in patients with smoking history

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Background: The impact of percutaneous coronary intervention (PCI) for chronic total occlusion (CTO) in patients with smoking history is not clear. Smoking history is known to have an adverse effect on clinical outcomes of coronary artery diseases. We evaluated the 12-month clinical outcomes between PCI and optimal medical therapy (OMT) for CTO lesions in patients with smoking history.
Methods: A total of 321 consecutive CTO patients with smoking history were divided into 2 groups according to treatment strategy; PCI group (n=145) and OMT group (n=176). Twelve–month clinical outcomes were retrospectively compared between the two groups.
Results: At baseline, patients in the OMT group had a lower left ventricular ejection fraction, and higher prevalence of elderly, cerebrovascular accident, peripheral vascular disease, congestive heart failure, left main disease, multivessel disease, right coronary artery CTO lesion, and collaterals ≥grade 2. Clinical outcomes at 12 months were similar between the 2 groups except lower mortality in the PCI group at univariate analysis. After baseline adjustment by multivariate analysis, 12-month mortality remained lower in the PCI group (OR 0.112, 95% CI 0.014-0.910, p=0.041) despite of increased target lesion revascularization (TLR) in the PCI group (table).

Table. 12-month clinical outcomes

Variables, n (%)	PCI (n=269)	OMT (n=301)	P Value (Unadjusted)	P Value (Adjusted)	OR (95%CI)
Mortality	9 (3.3)	24 (7.9)	0.018	0.041	0.112 (0.01-0.91)
Cardiac death	6 (2.2)	14 (4.6)	0.117	0.165	NS
Non cardiac death	3 (1.1)	9 (2.9)	0.120	0.994	-
Myocadial infaction; MI	6 (2.2)	15 (4.9)	0.082	0.503	NS
Q wave MI	5 (1.8)	9 (2.9)	0.384	0.729	NS
Non W wave MI	1 (0.3)	6 (1.9)	0.079	0.980	NS
Revascularization	27 (10)	23 (7.6)	0.313	0.253	NS
TLR	22 (8.1)	4 (1.3)	0.000	0.022	6.48 (1.31-32.03)
TVR	27 (10)	17 (5.6)	0.050	0.178	NS
Non TVR	2 (0.7)	7 (2.3)	0.130	0.483	NS
All MACE	36 (13.3)	45 (14.9)	0.593		
TLR MACE	28 (10.4)	20 (6.6)	0.106	0.186	NS
TVR MACE	36 (13.3)	41 (13.6)	0.934	0.994	NS

Adjusted by gender, age, myocardial infarction, hypertension, diabetes, chronic kidney disease, current smoker, multivessel disease, collateral vessels(≥grade 2), and failed CTO procedure.

Conclusions: In our study, PCI seems to be a favorable choice of therapy for CTO lesions in patients with smoking history in terms of reducing 12-month mortality. Long-term follow up with a larger study population will be necessary for further clarification.

LONG-TERM FOLLOW-UP IN CARDIOVASCULAR DISEASE

P6115 | BEDSIDE

The previous coronary heart disease mortality rates decrease stopped in the older age strata in the Czech Republic

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Objectives: Several recent studies in various countries have raised concern about a possible plateau or even reverse trend in CHD mortality in younger populations. CHD mortality rates have been decreasing in the Czech Republic since the mid-1980s, about 10 years later than in Western Europe, but quite rapidly. Plateauing in therapies uptake and adverse trends in some risk factors were documented recently. We aimed to assess the recent gender- and age- specific trends in CHD mortality in the Czech Republic.
Methods: Our analysis comprised the whole adult population of the Czech Republic aged 35-84 years, using mortality data from the Czech Bureau of Statistics. We compared the calculated age- standardized mortalities (European population standard) in 1989-2012 in 10- year age groups. CHD comprised International Classification of Diseases, 10th revision (ICD-10), codes I20-I25 and I44-I50 based on death certificates. Jointpoint Regression and log-linear Poisson regression models were used to estimate the annual change of mortality.
Results: The age standardized CHD mortality rates in men and women continued to decrease at a similar rate in the age groups of up to 55 years, the mortality decrease rate slowed down in the age groups of 55-74 since 2005 and virtually stopped to decrease in the age group of 75-84 already in 2000. This brought, due to the weight of CHD mortality in older age, the whole population CHD mortality decrease to a virtual halt. The trends were particularly obvious in chronic forms of CHD (I25), mortality from acute forms of CHD (I20-I22) continued to decrease linearly throughout the analyzed period in all age groups.
Conclusions: In contrast to studies from several other European countries, we found no plateauing of the CHD mortality rates in the age strata of 35-54 years in the Czech Republic. However, a plateauing of the mortality decrease was found in the older age strata and the decrease stopped in the 80+ olds. This brought, due to the weight of CHD mortality in older age, the whole population CHD mortality decrease to a virtual halt. The smaller reductions in mortality rates among older adults may be the result of delayed rather than averted CHD. Reducing preventable CHD risk factors and providing chronic CHD therapies is further vitaly important.
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P6116 | BENCH

Twenty five year trends in prevalence of cardiovascular risk factors among siberian adolescent population (1989-2014)

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Cardiovascular risk factors (smoking, overweight, hypertension and lipid disorders) are the major causes of morbidity and mortality in Russia. Control of the risk factors from adolescence may reduce cardiovascular events in adulthood. During the 1990s Russian population has been exposed to major political, economic and social changes.
Objective of the study was to assess trends in cardiovascular risk factors among siberian adolescents during the last 25 years.
Methods: Six cross-sectional population surveys of representative samples of schoolchildren aged 14-17 of both sexes were conducted from 1989 to 2014 in Novosibirsk (Russia). This time period included years of Russian reforms. Total study sample was 4011 adolescents (43% boys), response rate - 88-93%. Self-reported smoking (1 cig/week and more) was registered. Blood total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) were measured by enzymatic methods. Prevalence of dyslipidemia was evaluated with NCEP-peds criteria. Overweight was defined with the sex- and age-specific body mass index (BMI) cut-offs recommended by the IOTF. Hypertension (HT) was revealed with the National High Blood Pressure Education Program (4th report) criteria.
Results: During 1989-2014 the prevalence of regular smoking among boys declined from 45 to 18%, among girls - from 19 to 13%. Mean levels of TC decreased significantly in both gender groups. The greatest decreasing of mean values of TC was observed at the period from 1989 to 1999. Mean values of HDL-C for the 25-year period did not significantly changed. Frequency of hyper-

cholesterolemia during this time has fallen by more than 5 times. 25-year trends of HT have shown double decreasing during the reform period and stabilization in the post-reform time. Prevalence of HT was 5-fold increased in boys and 3-fold increased in girls from lowest BMI to highest.
Conclusion: Data from Novosibirsk indicate a downward trend in prevalence of smoking, overweight, hypertension and hypercholesterolemia in the adolescent population. This reducing of cardiovascular risk factors in adolescents can lead in 20-30 years to decreasing of cardiovascular morbidity and mortality in Siberia/Russia.

P6117 | BEDSIDE
Ten year cardiovascular disease and all-cause mortality: the Attica study

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Aims: The 10-year incidence of cardiovascular disease (CVD) and all-cause mortality, as well as its determinants, in a sample of men and women from Greece, was evaluated.
Methods: From May 2001 to December 2002, 1514 men and 1528 women (>18 y) without any clinical evidence of CVD or any other chronic disease, at baseline, living in greater Athens area, Greece, were enrolled. In 2011-12, the 10-year follow-up was performed in 2583 participants (15% of the participants were lost to follow-up). Incidence of fatal or non-fatal CVD (coronary heart disease, acute coronary syndromes, stroke, or other CVD) was defined according to WHO-ICD-10 criteria.
Results: The 10-year incidence was 14.3% in men and 9% in women ($p<0.001$). Multi-adjusted analysis revealed that increased age (Relative Risk (RR) per year = 1.07, 95%Confidence Intervals (CI):1.05-1.09), male gender (RR= 1.34, 95%CI: 0.80-2.27), diabetes (RR=1.69, 95%CI: 0.89-2.08) and C-reactive protein levels (odds ratio per 1 mg/dl = 1.08, 95%CI: 1.00-1.16), were the most significant risk factors, whereas adherence to Mediterranean diet (RR=0.96, 95%CI: 0.93-1.00), was the most important protective factor.
Conclusion: Incidence of CVD increased in Greece in the past 10 years, as compared with previous reports, despite the various prevention strategies and public health actions; adherence to the traditional diet still seems to be an effective, non-pharmacological mean for the reduction of disease burden.

P6118 | BEDSIDE
One-year outcomes in Asian patients with ST-segment elevation myocardial infarction, non-ST-elevation acute myocardial infarction and unstable angina: Observations from the EPICOR Asia study

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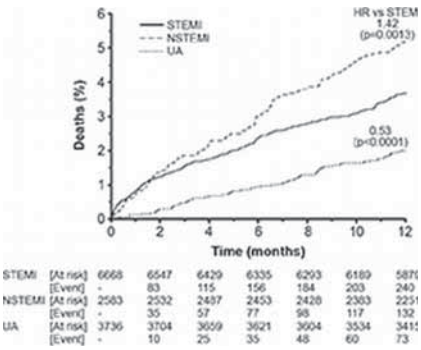
Background: Registry-based data suggest better short-term but worse long-term outcomes in NSTE-ACS than STEMI patients. Post-discharge outcomes data for ACS in Asia is sparse; 1-y ACS-related outcomes were studied.
Methods: EPICOR Asia (NCT01361386) is an ongoing prospective study of 12,987 consented hospital survivors of an ACS event from 219 centres in Asia. 1-y outcomes are reported based on final diagnosis of STEMI, NSTEMI, or UA.
Results: Patients (STEMI [6668], NSTEMI [2583], UA [3736]) were of mean age 60y, 76% were male, 53% had hypertension, 24% diabetes, 27% prior CVD, and 34% were current smokers. 1-year post discharge patient-reported outcomes are shown (Table); observed mortality was highest for NSTEMI (Figure).



Values are n (%)	STEMI (n=6668)	NSTEMI (n=2583)	UA (n=3736)	Total (n=12,987)
Coronary events	710 (10.6)	395 (15.3)*	523 (14.0)*	1628 (12.5)
Cardiac arrhythmia	25 (0.4)	8 (0.3)	20 (0.5)	53 (0.4)
Heart Failure	124 (1.9)	64 (2.5)	35 (0.9)*	223 (1.7)
Ischaemic stroke	31 (0.5)	25 (1.0)*	33 (0.9)*	89 (0.7)
Bleeding event	170 (2.5)	63 (2.4)	101 (2.7)	334 (2.6)
Thromboembolic event	456 (6.8)	239 (9.3)*	396 (10.6)*	1091 (8.4)
Death	240 (3.6)	132 (5.1)*	73 (2.0)*	445 (3.4)

*$p<0.05$ vs STEMI, log-rank test.

Conclusion: NSTE-ACS demonstrates more adverse outcomes than STEMI. Studies are warranted to identify better long-term management strategies in these patients.

P6119 | BEDSIDE
Secondary prevention in Jordan is underdeveloped and requires urgent improvement to meet the guidelines

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Purpose: CHD is a major health problem in Jordan and the leading cause of death, but little is known about the current provision and perceptions of Jordanian health care professionals' towards secondary prevention (SP) strategies. This study is designed to evaluate risk factors, explore the current provision of secondary prevention and health professionals' perceptions of SP for patients treated for established CHD in Jordan.
Method: A mixed methods repeated measures research design was used. 180 patients were recruited from 3 interventional hospitals after: acute myocardial infarction (AMI) treated medically; Percutaneous Coronary Intervention (PCI); and coronary artery bypass graft (CABG); then followed up 6 months later. The European guidelines on CHD prevention 2012 were used to compare against recommended targets. Semi-structured interviews with a purposive sample of 20 doctors and nurses from the 3 hospitals explored their perceptions of SP strategies.
Results: Of the 180 patients at discharge, 77% were obese or overweight, 59% were smokers, 59% had low levels of physical activity, 51% had elevated LDL, 44% were hypertensive and, 36% were diabetic. Of the 169 patients at follow up 75% were obese or overweight, 47% continued to smoke, 41% had low levels of physical activity and 25% had not controlled blood pressure. Recording of risk factor measurement at follow up was insufficient to evaluate achievement of therapeutic targets. Recording of risk factor history and current status was incomplete. No patients had psychological risk factors or dietary assessment. There was no cardiac rehabilitation, smoking cessation or secondary prevention available post discharge. The majority received brief physician advice about medications (72%) and smoking (49%). The use of prophylactic drug therapies was as follows: Aspirin 92%, lipid lowering drug 88%, beta-blockers 78%, ACE inhibitors 52% and statin 88%.
Interviews confirmed that while health professionals expressed the importance of secondary prevention, multiple barriers existed. They were generally unsatisfied with current SP provision and wanted to improve it, but identified particular training and other issues that need to be addressed in order to achieve this.
Conclusion: These findings confirm that despite extremely high prevalence of risk factors in this population, the provision of secondary prevention is poor and obstacles to its development are widespread. SP of CHD in Jordan requires urgent improvement and the contribution of nurses' to prevention should be enhanced to provide an effective, convenient and culturally sensitive SP services.

P6120 | BENCH
Long term follow up of factors influencing caregiver burden in partners of patients with heart failure

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Background: Due to aging populations in many countries worldwide and the fact that medical treatment for both acute myocardial infarction and heart failure have improved, patients with heart failure become older and live at home longer.
This has placed increased care responsibilities on families, who are being asked to shoulder greater care burdens for longer periods of time and many partners assume caregiving responsibilities without being aware of the burden interrelated with this role. Caregiver burden has been associated with physical and mental exhaustion, which often grow over time as the extent of caregiving demands increases.
Aim: To examine caregiver burden over time during 24 months follow-up in partners to patients with heart failure receiving a psycho-educational intervention compared to a control group, and to describe the long-term effect of morbidity and mortality among partners.

Method: A randomized study design with patient-partner dyads affected by heart failure with a follow-up assessment after 24 months. The intervention included a nurse-led psycho-educational 3-session program.
Result: 155 dyads were included and 96 partners concluded the 24 months assessment. The intervention did not show any significant differences in any dimension in caregiver burden among the partner dyads after 24 months. After 24 months follow up the total caregiver burden had increased significantly in both groups compared to baseline (36 vs 38, $p<0.05$).
Partners in both the intervention and control group reported decreased physical health between the baseline assessment and the 24-month follow-up. However, those in the intervention group had a significantly greater decrease in both PCS (B= -4.13, t(90)= -2.43, $p<0.05$), and physical functioning (B= -6.76, t(93)= -2.21, $p<0.05$).
There was no significant difference between the groups in the number of admissions in hospital or number of days in hospital during the follow up period. Admission within 24 months occurred in 13% of the partners (n=9) in the intervention group and in 24% (n=19) in the control group.
Conclusion: This study is the first long-term follow up of caregiver burden in partners to patients with HF describing an increase in several aspects of this burden over time. To identify caregivers that experience high caregiver burden and target those with support and interventions can lead to a significant improvement in caregiver wellbeing.

P6121 | BEDSIDE
Carotid artery intima-media thickness and ideal cardiovascular health. The Paris Prospective Study III

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Purpose: Carotid intima-media thickness (cIMT), a structural component of the arterial remodelling, has been repeatedly associated with the onset of cardiovascular (CV) disease and is widely sued as a surrogate marker of CV disease. In 2010, the American Heart Association's 2020 Strategic Goals defined a new concept of ideal CV health composed of 7 modifiable health metrics in order to prevent CV disease. We hypothesized that ideal CV health status would be associated with thinner cIMT.
Methods: We included 5126 men and women aged 50-75 years who enrolled in the Paris Prospective Study III (PPS3) from 2008 to 2011 and who were free of overt CV disease and treatment. The CV health status was defined as poor (0 or 1 health metric present), intermediate (2, 3 or 4) and ideal (5, 6 or 7). cIMT was measured in the right common carotid artery in an area free of carotid plaques using carotid echo tracking, a highly accurate method with 20 micrometers precision. The likelihood of a thinner cIMT (sex specific first quartile) associated with CV health status was explored by logistic regression analysis.
Results: Mean age was 58.9 years and 60.6% were men. The median cIMT was 623μm (IQR: 548, 707) in men and 629μm (IQR: 559, 697) in women respectively. The prevalence of ideal CV health status decreased (29.49%, 26.35%, 24.22%, 19.94%) while that of poor CV health status increased (13.42%, 20.33%, 29.18% and 37.07%) with cIMT (P for trend <0.001). After adjusting for age and sex, participants with intermediate (OR: 1.67, 95% CI [1.35-2.07], $P<0.001$) and ideal (OR: 2.24, 95% CI [1.72- 2.92], $P<0.001$) CV health status were more likely to have a thinner cIMT (first quartile) respectively.
Conclusion: By showing that subjects with ideal CV had a two-fold increased odds of having a thinner cIMT, the current data support the benefit of promoting primordial prevention of CV disease.

P6122 | BEDSIDE
Secondary medical prevention and clinical outcome in coronary artery disease patients with a history of vascular intervention: a report from the CORONOR investigators

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Aim: To assess the level of secondary prevention and the outcome of coronary artery disease (CAD) patients who have a history of vascular intervention.
Background: Patients with polyvascular disease have been reported to receive less evidence-based medications, with worse risk factor control, and to be at higher risk than patients with single-bed disease. It is unknown whether these findings remain valid in the modern era of secondary prevention.
Methods: We included 4184 patients with stable CAD. Two groups were formed according to the absence (n=3704) or presence (n=480) of a history of non-coronary vascular intervention. Treatments and risk factor control were recorded at inclusion. Follow-up was performed after 2 years.
Results: Antiplatelets, angiotensin system antagonists, beta-blockers, and statins were widely prescribed in both groups. The number of antihypertensive drugs was higher in patients with vascular intervention. Except for slight increases in the rate of current smokers and in systolic blood pressure, risk factor control was similar between groups. All-cause and cardiovascular mortality rates were higher in patients with vascular intervention ($P<0.0001$) with adjusted HR of 1.69 [1.24-2.32], and 2.20 [1.39-3.48], respectively.
Conclusions: In modern practice and real life conditions, the higher risk of CAD patients with a history of vascular intervention is well taken into account, with more intense secondary prevention and similar risk factor control than patients without such history. Despite this, however, these patients remain at higher risk of events. This should be an incentive to discuss more stringent objectives for secondary prevention in patients with polyvascular disease.

P6123 | BEDSIDE
Clinical characteristics of young atrial fibrillation patients: From one-year follow-up of the Fushimi AF Registry

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Purpose: Atrial fibrillation (AF) is a common arrhythmic disorder among the elderly, and is increasing significantly as the population ages (reportedly 0.6% of total population in Japan). Stroke is a devastating complication of AF, and advanced age is a well-known risk for stroke. However, clinical characteristics of young AF patients have not been well described.
Methods: The Fushimi AF Registry, a community-based prospective survey, was designed to enroll all of the AF patients in Fushimi-ku, Kyoto, Japan. Fushimi-ku is densely populated with a total population of 283,000, and is assumed to represent a typical urban community in Japan. At present, we have enrolled 3,821 patients (1.4% of total population) from March 2011 to December 2013. One-year follow-up was completed in 2,966 patients as of December 2013.
Results: Young AF patients (<65 year of age; n=517, 17.4% of total) were less likely to have major co-morbidities compared with others (n=2,449); congestive heart failure (young vs. others: 17.6% vs. 28.9%; $p<0.01$), hypertension (50.7% vs. 63.5%; $p<0.01$), diabetes mellitus (21.1% vs. 24.1%; p=0.15) and previous stroke (10.3% vs. 21.2%; $p<0.01$). Therefore, CHADS2 score was lower in the young (1.12 ± 1.05 vs. 2.25 ± 1.31; $p<0.01$), and they received much lower anticoagulation therapy (42.8% vs. 52.8%; $p<0.01$). Moreover, guideline adherence in PT-INR control for patients taking warfarin (the Japanese guideline recommends 1.6-2.6 for patients ≥70 years of age, and 2.0-3.0 for those <70) was much lower in young AF patients; the proportion of patients within target PT-INR range was 29.1% in the young and 58.9% in the others.
During one-year follow-up, the incidence of stroke was 1.5% (n=8) in the young, and 2.8% (n=68) in the others. Of 8 young stroke patients, 5 had not received oral anticoagulants (4 patients were CHADS2 score 0 or 1, 1 patient was 2). Among the young, the incidence of stroke was considerably high in patients with CHADS2 score ≥3 (3/58, 5.2%), compared with those with CHADS2 score 0-2 (5/459; 1.1%).
The incidence of major bleeding in the young patients was low (4/517, 0.8%) compared with that in the others (42/2,449, 1.7%; p=0.12).
Conclusion: Young AF patients have smaller risk profiles for stroke, and the incidence rate of stroke was low indeed, but it cannot be neglected especially for those with high CHADS2 score. A better risk stratification scheme, and better management is definitely needed for young AF patients.

P6124 | BEDSIDE
A comparison of cardiac event rates in patients with or without multiple myeloma in the US

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Background: Multiple myeloma (MM) patients have age-, disease-, and treatment-related risk factors for cardiac events; it is unknown if this risk is greater than in non-MM patients.
Methods: Two cohorts were identified in the 2006–2011 MarketScan database: 1) MM patients treated with corticosteroids and ≥3 drugs (bortezomib, IMiDs, and alkylating agents or anthracyclines), where the index date (ID) was the date criteria of exposure to the 3 drugs was met; and 2) age and sex matched No-MM patients (5:1); the distribution of No-MM patients' IDs matched MM patients. Baseline was 6 months prior to the ID. Patients were followed from ID to study end. Baseline variables included age, sex, geographic area, and comorbidities. Incidence was calculated for patients without the event(s) at baseline. Hazard ratios (HR) and 95% confidence intervals (CI) were adjusted for baseline variables when univariate analyses showed a 10% difference.

Results: 1,723 MM patients and 8,615 comparators were analyzed. Median (range) months of observation were: MM cohort, 9 (0–60); no-MM, 19 (0–66). Prevalence of cardiac events was greater in the MM (52%) vs. no-MM group (35%), P<0.0001. Incidence of any cardiac event, arrhythmia, congestive heart failure (CHF), cardiomyopathy and conduction disorders was also significantly greater among MM vs. no-MM patients; the incidence of hypertensive/arterial events and ischemic heart disease was similar for MM and no-MM patients (Table).

Hazard ratios for cardiac events

Cardiac event	Adjusted HR (95% CI)
Any	2.2 (1.9–2.5)
Cardiac arrhythmia	4.1 (3.5–4.8)
Congestive heart failure	2.9 (2.2–3.7)
Cardiomyopathy	2.6 (1.8–3.8)
Conduction disorders	1.7 (1.2–2.5)
Hypertensive/Arterial	1.1 (1.0–1.3)
Ischemic heart disease	1.0 (0.8–1.3)

Conclusions: This study provides the first comparison of cardiac event risk in MM patients vs. age- and gender-matched patients without MM. Cardiac event prevalence and risk was greater in MM patients with ≥3 prior drugs for any cardiac event, arrhythmia, CHF, cardiomyopathy, and conduction disorders vs. patients with no MM.

P6125 | BEDSIDE
Cross-sectional cardiac rehabilitation with a Nurse Case Manager (GoHeart) improves risk factors, self-care and psychosocial outcomes. A 1-year follow-up study

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Background: In Denmark the local and regional health authorities share responsibility for cardiac rehabilitation (CR). The aim of this study was to assess effectiveness of cross-sectional CR coordinated by a nurse case manager.
Design and methods: The Danish single-centre rehabilitation programme (GoHeart) was evaluated in a cohort study in consecutive patients admitted to CR at our hospital from 2010 to 2011. The criteria for CR were the event of acute myocardial infarction or stable angina leading to assessment of invasive revascularization (LVEF ≥45%). The rehabilitation status was assessed at admission (phase IIa), at 3 months at discharge from hospital (phase IIb) and at 1-year follow-up (phase III). Outcomes were cardiac risk factors measured objectively and by self-report, stratified self-care status and self-reported psychosocial factors (SF-12 and HADS). Intention-to-treat and predefined subgroup analysis on gender were performed.
Results: 183 of 241 (75.9%) patients were included (mean age 63.8 years). At discharge improvements were found in total-cholesterol (p<0.001), LDL (p<0.001), functional capacities (METS, p<0.01), self-care management (p<0.001), SF12 (physical; p<0.001 and mental; p<0.01) and in depression symptoms (p<0.01). At 1-year follow up these outcomes were maintained; in addition there was improvement in BMI (p<0.05), and HDL (p<0.05). Some variables deteriorated at 1 year; an increase in diastolic blood pressure (p<0.001) and a decrease in SF12, pcs (p<0.01). There were no gender differences.
Conclusion: Cross-sector cardiac rehabilitation led by a nurse case manager improves overall risk factors, self-care and self-reported psychosocial factors. Further improvements in most variables were seen 1 year after providing evidence of the benefits of shared care cross sectors. No differences in gender were found suggesting that GoHeart may be the CR program to enhance women compliance, which otherwise can be a challenge in cardiac rehabilitation.

MECHANISMS OF THE PROGRESSION ON HYPERTENSION

P6127 | BENCH
Long-term exercise alleviates hypertension and improves vascular redox state via upregulating Glrx-1 in spontaneously hypertensive rats

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Aim: Glutaredoxin-1 (Glrx-1), a redox-regulator of thioredoxin superfamily, plays an important role in the redox signaling of cardiovascular diseases. Our previous studies showed that exercise training in young spontaneously hypertensive rats (SHRs) can delay the development of hypertension. The objective of the present study was to investigate the role of Glrx-1 in exercise-generated anti-hypertensive effects in SHRs.
Methods: Eight-wk-old male SHR were divided into sedentary (SHR-Sed) and exercise group (SHR-Exe) which were subjected to a single bout of aerobic treadmill running at 20 m/min, 1 h/d for 16 wks. Age-matched Wistar–Kyoto rats were used as normotensive control groups (WKY-Sed and WKY-Exe). Blood pressure was determined by the tail-cuff method and mesenteric artery function was assessed with DMT myograph system. Vascular total reactive oxygen species (ROS) were determined by DHE staining, mesenteric vascular GSH, GSSG and NO production were measured spectrophotometrically.
Results: SHR subjected to 16-wk treadmill training exhibited significantly lowered systolic blood pressure (P<0.01) and enhanced vasorelaxation of mesenteric artery (P<0.01) to ACh as compared with their sedentary counterparts, whereas exercise did not affect blood pressure and vasorelaxation of mesenteric artery in WKY rats. Long-term exercise increased vascular Akt and eNOS phosphorylation and NO production in both SHR and WKY rats. Although mesenteric vascular Glrx-1 levels were similar in sedentary SHR and WKY, exercise training significantly increased vascular Glrx-1 expression in SHR (2.05±0.24-fold, P<0.01) but not in WKY rats. Moreover, exercise training increased GSH/GSSG ratio (SHR-Exe 12.35±0.53 vs. SHR-Sed 0.73±0.21, P<0.01), together with reduced ROS level in SHR.
Conclusions: These results demonstrate that long-term exercise improves vascular redox state and mesenteric vascular function via up-regulating vascular Glrx-1.

P6128 | BEDSIDE
Cardiovascular risk in relation to a five-tiered classification of hypertensive left ventricular geometric abnormalities: the Campania-Salute Network (CSN)

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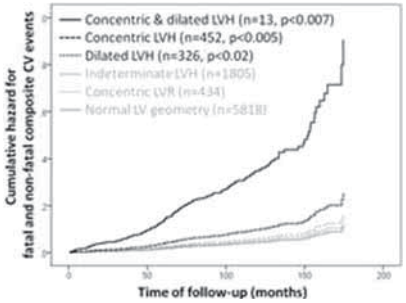
Purpose: The Dallas Heart Study has extended our left ventricular (LV) geometric classification by introducing new categories of dilated LV hypertrophy (LVH). We tested prognostic impact of the new classification.
Methods: We evaluated baseline parameters of 8848 hypertensive participants to the Campania Salute Network (53±12 yrs, 56% men, 42% obese), free of prevalent cardiovascular (CV) disease, with ejection fraction≥50%. Cut points for LVH (LV mass index [LVMi, g/m$^{2.7}$]), concentricity (relative wall thickness) and dilatation (LV end-diastolic dimension, [LVIDDi, cm/m]) were derived from a reference population. Incident CV events were: fatal or non-fatal myocardial infarction or stroke, coronary revascularization or transient ischemic attack).
Results: LV and left atrial dimensions (LAd), stroke index and cardiac index were increased in all LVH subtypes, and reduced (except LAd) in concentric LV remodeling (LVR). LVMi was increased in all abnormal LV geometric patterns, especially in the LV dilated patterns. Estimates of vascular impedance and resistance were higher in the presence of concentric LV remodeling or LVH, lower with indeterminate or dilated LVH, and normal in the presence of concentric-dilated LVH (all p<0.05). Age and sex-adjusted hazard for composite end-points was significantly higher for dilated LVH (HR=1.9, 1.1-3.3), concentric LVH (HR=1.9, 1.2-3.0), and concentric-dilated LVH (HR=6.8, 1.7-27.8, all p<0.02), but not for indeterminate LVH or LVR (figure).



Conclusion: Consideration of LV dilatation in the evaluation of LV geometry-related CV risk indicates the importance of volume load coexisting witht hypertensive pressure overload. At a given normal ejection fraction, the balance between the two load components is linked with the shape of LV geometric adaptation.

P6129 | BEDSIDE
Correlation between dysfunction of different hemostatic links and microalbuminuria in patients with arterial hypertension

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Aim: To establish the relationship between activity of different hemostatic links and presence of microalbuminuria in patients with arterial hypertension.
Material and methods: 60 patients with arterial hypertension (grade 2) were examined: 1st group included 22 patients with microalbuminuria, 2nd group included 38 patients without microalbuminuria. Among patients prevailed age group 50-59 years (40%).Venous blood samples were drawn from the cubital vein after an overnight fasting and were examined for: 1)platelet hemostasis 2)coagulation

activity: Activated Partial Thromboplastin Time (aPTT), Thrombin Time (TT), Soluble Fibrin-Monomer Complexes (SFMC) 3)fibrinolytic activity: XII-a dependent fibrinolysis; 4)anticoagulation activity: Antithrombin III, Protein C.
Results: By level spontaneous aggregation and platelet aggregation with ADP was not observed statistically significant differences between the two study groups. However, the analysis of platelet aggregation with epinephrine attracted attention more pronounced changes in the group with MAU. So, the degree of aggregation with epinephrine in the group with MAU was 2.6 times higher than in the group without MAU ($p<0.05$). It was noted also change the speed of platelet aggregation with epinephrine, which in patients with MAU was higher at 2.54 times ($p<0.05$). 1st group of patients exhibited acceleration of aPTT (14,4% shorter in comparison to aPTT of the 2nd group (p=0,041)), acceleration of TT (11,5% shorter in comparison to TT of the 2nd group (p=0,04)). It was found that by content of SFMC observed a statistically significant difference between the groups with the presence and absence of MAU. So in patients with MAU level of SFMCincreased in 1.56 times relative to the comparison group. In patients with MAU inhibition of XII-a dependent fibrinolysis was 1.45 times higher than in the group without MAU. Noteworthy that the content of natural anticoagulants - antithrombin III and protein C was significantly lower in both groups of patients.
Conclusions: Microalbuminuria in patients with arterial hypertension is associated with activation of thrombin and fibrin formation, and reduction of anticoagulation potential, which proves significance of microalbuminuria in development of thrombotic complications in this group of patients.

P6130 | BEDSIDE
Clinical characteristics of patients with resistant hypertension in Greece: Data from a multi-center national registry

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Purpose: Resistant hypertension is related with adverse cardiovascular prognosis, whereas there are scarce data regarding its clinical characteristics in Greece. The aim of this national registry was to identify and analyze cases of resistant hypertension in Greece.
Methods: For this purpose we studied 340 patients with resistant hypertension [office blood pressure (BP) $\geq$140 and/or 90 mmHg despite the use of $\geq$3 antihypertensive drugs at maximum tolerated doses including one diuretic) who participated in the Greek multi-center HERHODOTOS registry. From all participants data were collected regarding office and home BP, renal function, current antihypertensive treatment and clinical comorbidities.
Results: Resistant hypertensive patients (mean age: 68 years, 183 males, office BP: 158/87$\pm$18/11 mmHg, heart rate 70$\pm$19 bpm under 4.4$\pm$0.6 drugs) exhibited high body mass index (30.9$\pm$3.8 kg/m^2) and 30% were smokers. In the whole population, home BP was 149/84$\pm$18/10 mmHg while creatinine values were 1$\pm$0.3 mg/dl. Severe resistant hypertension (office systolic BP$\geq$160 mmHg) was present in 39.2%. Regarding clinical comorbidities, 12% of the registered patients suffered from sleep apnea, 36% had diabetes mellitus and 54% exhibited dyslipidemia. The prevalence of coronary heart disease was 28%, while stroke and heart failure was present in 6% and 8% of the patients respectively. Chronic kidney disease was found in 11% of the resistant hypertensives, while 4% suffered from peripheral arterial disease and 16% from atrial fibrillation.
Conclusions: The present registry shows that in a Greek population of resistant hypertensive patients there is a high prevalence of severe resistant hypertension, coronary heart disease and atrial fibrillation. Our findings improve understanding of the clinical phenotype of resistant hypertension in Greece and could contribute in better clinical management of these high risk patients.

P6131 | SPOTLIGHT
Prediction of total mortalityin patients with Hypertension

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Objective: To model the high risk group of total mortality in patients with hypertension (HT) living in an urban area.
Design and methods: We conducted a 10-year prospective cohort study of 1070 patients with hypertension living. The participants were examined in 1999 (1st survey) and 2009 (2nd survey). The research included standard questionnaires for detection of cardiovascular risk factors, blood pressure measurement, electrocardiography, echocardiograph and cholesterol data. The total mortality data for the period of 10 years were analyzed. The logistic regression model was used to show the relation between essential risk factors in patients with HT and total mortality.
Results: In 10 years, we had 336 cases of death. Comparative analyses did reveal significant difference in total mortality between men and women during a ten-year period (35.1% vs. 27.8% respectively, $p<0.01$). Multifactor model of significant risk factors of total mortality included a high ($\geq$29.0 kg/m^2) index of body mass ($p<0.001$), high (SV1+Rv5-v6 $\geq$35 mm) hypertrophy of the left ventricle according to ECG signs ($p<0.001$), non-optimal ($<$4.9 mmol/l or $>$6.2 mmol/l) glucose level ($p<0.001$), myocardial infarction in the history case ($p<0.001$), alcohol abuse ($p<0.01$), a high ($\geq$3.8 mmol/l) level of cholesterol of low density lipoproteins ($p<0.01$), diabetes mellitus ($p<0.01$), a high ($>$100 μmol/l) creatinine level ($p<0.01$), moderate (28 mm $\leq$ SV1+Rv5-v6 $\leq$34 mm) hypertrophy of the left ventricle based on ECG signs ($p<0.01$), absence of higher education ($p<0.05$), a high ($\geq$150 mmHg) level of systolic blood pressure ($p<0.05$), stroke in the history case ($p<0.05$), high ($\geq$85 beat/min) frequency of heart rate ($p<0.05$), hypertrophy of the left ventricle based on echocardiographic signs ($p<0.1$), smoking ($p<0.1$). The proposed multifactor model permits to separate a group of non-significant, low and high risk of total mortality.
Conclusion: Using risk factor population norms, the multifactor model predicting the relative risk total mortality in hypertensive patients was suggested.

P6132 | BEDSIDE
Influence of climatic factors on recourse of patients with arterial hypertension in emergency department

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Purpose: To determine the relationship between climatic factors and the recourse of patients with arterial hypertension (AH) in the emergency department.
Methods: 1477 cases of appeals in the emergency department of Perm city hospital about AH in 2012 year were registered. Fluctuations and averages of climatic factors (temperature, barometric pressure, relative humidity, wind speed) were determined every day during this year. Cross- tables, indexes Pearson Chi-square and Cramer's V were used to assess the results. Data are presented as mean $\pm$ standard deviation.
Results: The largest numbers of cases of AH was in spring (391) and in winter (383). Maximum number of appeals was in March (148) and in January (147). Among the 1477 patients admitted to the emergency department were 25% men and 75% women. It was found that the number of appeals was higher in people aged from 70 to 80 years. Average age of men with AH was 58.1$\pm$15.5 years and women with AH was 65.1$\pm$13 years. The peak of hypertensive patients in the emergency department was registered at 11.00-12.00 a.m. and at 9.00-10.00 p.m. Average systolic blood pressure was 182$\pm$23 mm Hg and average diastolic blood pressure was 98$\pm$12 mm Hg. There was a significant relationship between the number of calls and temperature fluctuations (Cramer's V=0,32; $p<0,001$). Significant relationships with barometric pressure fluctuations (Cramer's V=0,24; $p<0,001$), variations in humidity (Cramer's V=0,24; $p<0,001$) and mean wind speed (Cramer's V=0,27; $p<0,001$) were determined too. There were no relationships between recourse numbers and the average temperature, average pressure, average humidity and wind velocity fluctuations. But it was found that the number of appeals increase when the relative humidity level was more than 71%.
Conclusions: Moderate forces relationship was marked between instability of weather conditions and recourse of patients with AH to the hospital. Particularly this relationship was noted for such values of climatic factors as temperature fluctuations, pressure fluctuations, fluctuations in humidity and average wind speed. Perhaps relationship will be stronger if we consider the combination of several factors simultaneously.

P6133 | BEDSIDE
Comparison of echocardiographic characteristics in patients with normotension, white coat hypertension, masked hypertension, and sustained hypertension

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Background: We investigated the echocardiograpic characteristics in patients with normotension (NT), white coat hypertension (WCHT), masked hypertension (MHT), and sustained hypertension (SHT) by clinic BP and ABPM.
Methods: This study is a retrospective analysis of patients with ABPM from January 2008 to May 2013. After measurement of clinic BP and ABPM, 4 groups of patients were identified namely: (i) NT: BPs are normal both clinically and by ABPM); (ii) WCHT: clinical BP were above limits, but ABPM were normal; (iii) MHT: clinical BP were normal, but ABPM were high; (iv) SHT: both office and ABPM were high.
Results: In total 75 patients with NT (mean age 46.5$\pm$13.7 years, female 32%), 34 patients with WCHT (mean age 51.6$\pm$13.9 years, female 50%), 201 patients

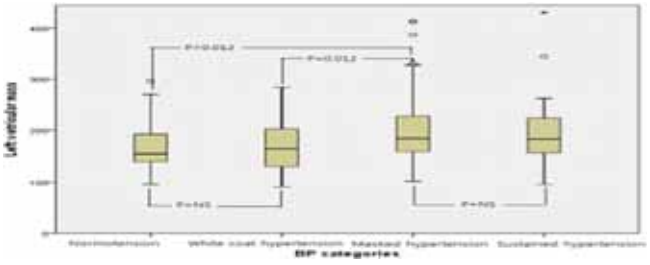

Figure 1

with MHT (mean age 48.2±12.9 years, female 44.8%), and 83 patients with SHT (mean age 49.5±13.9 years, female 44.6%) were included. In echocardiographic findings, Subjects with NT and WCHT had similar, and also subjects with MHT and SHT had similar. MHT had significant higher relative wall thickness (RWT) (p=0.047, p=0.002), and LV mass (p=0.012, p=0.012) than NT and WCHT. WCHT had lower RWT (p=0.007) and LV mass (0.047) than SHT. There were no significant differences in LV ejection freaction and left atrial diameter.
Conclusion: MHT had significant cardiac damage than NT and WCHT. This results showed ABPM is more predictive of target organ damage to clinical BP, and patients with MHT should be carefully follow up about the elevated cardiaovascular risk.

P6134 | BEDSIDE
Blood pressure and incidence of twelve cardiovascular diseases; lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people

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Background: The associations of blood pressure (BP) with the different manifestations of incident cardiovascular disease (CVD) in a contemporary population have not been compared.
Methods: Using linked electronic health records from 1997 to 2010,we assembled a cohort of 1.25 million initially CVD-free patients aged ≥30 yrs, a fifth of whom received BP-lowering treatments. We studied the heterogeneity in the age-specific associations of clinic BP with twelve acute and chronic cardiovascular diseases, and estimated lifetime risks (to age 95) and CVD-free years of life-lost (YLL) adjusted for other risk factors at index ages 30, 60 and 80 years.
Findings: Over 5.2years median follow-up 83098initial CVD presentations were recorded. In each age group the lowest risk was among people with systolic blood pressure (SBP) of 90–114 mmHg and diastolic blood pressure (DBP) of 60–74 mmHg. Associations were monotonic increasing or null depending on the disease and age-group. Compared to the age- and sex-adjusted association of SBP (HR per 20 mmHg increase) with total CVD (1.28 [95% CI 1.27–1.29])associations were markedly stronger for intracerebral haemorrhage (1.44 [1.36–1.53]), subarachnoid haemorrhage (1.42 [1.32–1.55]) and stable angina (1.41 [1.38–1.44]), and markedly weaker for abdominal aortic aneurysm (AAA; 1.08 [1.03–1.13]). Pulse pressure associations were protective for AAA (HR per 10mmHg 0.91 [95% CI, 0.88–0.95]) and strongest for PAD 1.23 [95% CI, 1.21–1.25]. People with hypertension (BP ≥140/90 mmHg or BP treatments), had a lifetime risk of total CVD at age 30 of 63.3% (62.9–63.8) (vs. 46.1% [45.5–46.8] for those without) and developed CVD 5.0 (4.8–5.2) years earlier. Stable and unstable angina accounted for most (43%) of the CVD-free YLL associated with hypertension from index age 30, whereas heart failure and stable angina accounted for the largest proportion (19% each) of YLL from index age 80.
Interpretation: The widely held assumptions that blood pressure shows strong associations with the incidence of all cardiovascular diseases across a wide range of ages and that diastolic and systolic associations are concordant are not supported by this high resolution study. The heterogeneity of blood pressure associations needs to be considered in efforts to tackle the substantial lifetime burden of hypertension which persists despite current medication.

P6135 | BEDSIDE
Serum uric acid and incident hypertension in a long term prospective cohort of young and middle-aged males

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Objective: Serum uric acid (SUA) is known as a predictor of future hypertension. However, subgroups that are associated with higher risk for future hypertension remains unknown.
Method: We conducted a long term prospective cohort study to examine the relationship of SUA to the onset of hypertension in large number of males. Males aged 18-60 (n=28,951) without prevalent hypertension at baseline were enrolled in 2000. All subjects took an annual medical checkup until 2010. The participants were categorized into 3 groups according to the tertile of SUA concentration (1st:reference, 2nd, and 3rd). Incident hypertension was defined as newly detected blood pressure ≥140/90 mmHg and/or initiation of antihypertensive drugs. Subgroup analyses were performed in groups split at age (<40 vs. ≥40 years) and body mass index (BMI) (<25 kg/ m^2 vs. ≥25 kg/ m^2).
Result: During a median follow-up time of 9.4 years, there were 12,954 cases (45%) hypertension. Median SUA concentration (mg/dl) at baseline in each group were 1st tertile 4.7 (0.1-5.4), 2nd tertile 5.9 (5.5-6.3), and 3rd tertile 7.1 (6.4-13.1), respectively. The cumulative incident hypertension rate was significantly higher in 3rd tertile (53.7%)than in the 1st tertile (38.8%). The adjusted hazard ratio [95% confidence interval] for incident hypertension was HR: 1.00 [0.96-1.05] in the 2nd tertile, HR: 1.15 [1.10-1.21] in the 3rd tertile, respectively. In subjects in ≥40 years old group and those with BMI <25 kg/m^2 group, the 3rd SUA group showed higher HRs:1.23 [1.14-1.32] and 1.17 [1.11-1.24]), respectively.

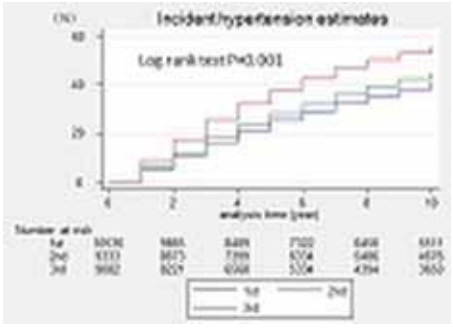

Figure 1

Conclusion: Higher SUA concentration was associated with future hypertension in young and middle-aged males. This association was higher among men with a ≥40 years old and BMI <25.0 kg/m^2 group.

PROGRESSION IN HYPERTENSION

P6137 | BEDSIDE
Increased oxidative stress predicts future development of hypertension in male general population

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Purpose: Oxidative stress is considered to be associated with several cardiovascular disorders including the process of atherosclerosis. The present study tested the hypothesis that increased oxidative stress predicts future development of hypertension, one of the major risk factors of cardiovascular diseases, in the general population.
Methods: Serum levels of derivative reactive oxygen metabolites (d-ROM), a marker of oxidative stress, were measured in non-smoking normotensive 2,106 subjects who visited our hospital for a physical check-up (male=38.2%, 55.2±10.9 year-old). Their blood and urine were sampled early in the morning after overnight fasting and serum d-ROM was measured using colorimetric assay (Diacron, Italy). After baseline examination, they were followed up for the median of 1,106 days with the endpoint being the development of hypertension. Hypertension was defined as systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90mmHg, or the use of antihypertensive medications. The exclusion criteria were: ischemic heart disease, valvular heart disease, congestive heart failure, atrial fibrillation, inflammatory disease, and malignant disease.
Results: During the follow-up, hypertension developed in 419 subjects (66.7 per 1000 person-year), with the incidence being more frequent in male than female subjects (83.2 vs. 56.8 per 1000 person-year). Incident hypertension was increased across the tertiles for baseline levels of oxidative stress in male (69.8, 78.6, and 102.1 per 1000 person-year in the first, second, and third tertiles, respectively, p<0.05), but not female, subjects. The hazard ratios of incident hypertension (first quartile as a reference) in male subjects was 0.951 (95% confidence interval 0.661-1.369) and 1.440 (1.010-2.054) in the second and third tertiles, respectively, after adjustment for possible factors. Multivariate Cox hazard analysis, where d-ROM was taken as a continuous variable, indicated a significant correlation between d-ROM levels at baseline and future incidence of hypertension in male (hazard ratio 1.004; 95% confidence interval 1.001-1.006), but not in female subjects.
Conclusions: In male general population, increased oxidative stress evaluated by d-ROM levels was significantly associated with the future development of hypertension. Oxidative stress may be involved in the process of developing hypertension.

P6138 | BEDSIDE
Morning central blood pressure surge is lower than morning peripheral blood pressure surge in untreated hypertensives

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Morning blood pressure (BP) surge is considered to be an independent risk factor for cardiovascular diseases. On the other hand, there is increasing evidence that central systolic pressure (CSP) is stronger correlated with target organ damage and cardiovascular events than peripheral systolic pressure. Therefore, the aim of study was to evaluate the relationship between morning central and peripheral BP surge.
Methods: Fifty patients with newly diagnosed, never treated hypertension (age 40.4±11.5 years, 35 men) and 50 normotensive subjects (matched for age and sex) were included into the study. Applanation tonometry of the radial artery has

been used to derive 24-hour CSP (BPro, HealtStats). Peripheral BP was measured using Spacelabs device. For analysis of the morning surge (MS) in BP, we determined the awake and asleep periods from the subjects' diary cards. The sleep-through MS was the difference between the morning pressure (the average BP during the 2 hours after awakening) and the lowest nighttime BP (the average of the lowest pressure and the 2 readings immediately preceding and after the lowest value). The preawakening MS was the difference between the morning blood pressure and the preawakening BP (the average BP during the 2 hours before awakening).
Results: The 24-hour CSP was 129.5±10.6 mmHg in hypertensives and 110.5±12.4 mmHg in normotensives ($p<0.05$). The average daytime and nighttime CSP was 133.8±11.1 mmHg and 123.1±11.1 mmHg ($p<0.05$) in hypertensives whereas 114.3±13.7 mmHg and 104.8±11.7 ($p<0.05$) in normotensives, respectively. The corresponding peripheral systolic pressure was 141.5±7.6 mmHg vs. 124.7±9.4 mmHg ($p<0.05$) in hypertensives and 126.0±6.6 mmHg vs. 109.6±7.9 mmHg ($p<0.05$) in normotensives. The values of morning BP surge are presented in the table.

The mean values (±SD) of morning surge

	Peripheral sleep-through MS	Central sleep-through MS	p	Peripheral preawakening MS	Central preawakening MS	p
Hypertensives (n=50), mmHg	24.07±11.87	18.59±7.33	0.006	16.88±9.06	12.25±7.19	0.006
Normotensives (n=50), mmHg	21.83±8.84	17.52±13.22	0.058	18.30±9.15	12.04±13.69	0.008
p	0.29	0.62		0.44	0.92	

SD, standard deviation; BP, blood pressure; MS, morning surge.

Conclusion: Central sleep-through MS and preawakening MS are significantly lower than peripheral sleep-through MS and preawakening MS in hypertensives. In normotensives only central preawakening MS is lower than peripheral preawakening MS.

P6139 | BEDSIDE
Circadian variation of acute aortic dissection: significance of blood pressure dipping pattern

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Purpose: Acute aortic dissection (AAD) is a life threatening cardiovascular disease with high mortality. Hypertension has been known to be a risk factor of AAD. However, little is known about the association between the onset-time of AAD and circadian variation of blood pressure (BP). The purpose of this study was to clarify the characteristics of circadian variation of BP in AAD and its relation to the onset time of this disease.
Method: This study included type B spontaneous AAD patients who were referred to our institution and treated conservatively between January 2008 and June 2013. Patients with type A AAD, secondary to trauma, and type B AAD which was preceded surgical intervention were excluded.
Results: There were 115 patients with spontaneous type B AAD in the study period. Thirty-nine patients did not receive ABPM during admission. Eight patients were excluded because the onset-time could not be identified certainly. Finally, Sixty-eight patients with type B AAD were enrolled in this study. The distribution of circadian patterns in the study patients were as follows: extreme-dipper, 0% (none); dipper, 20.6% (n=14); non-dipper, 50% (n=34);riser, 29.4% (n=20). Non-dipper and riser pattern were more frequently observed compared with other population studies reported previously. Moreover, no patient in dipper group had night-time onset while 31.5% of the patients in non-dipper group had it (p=0.01).

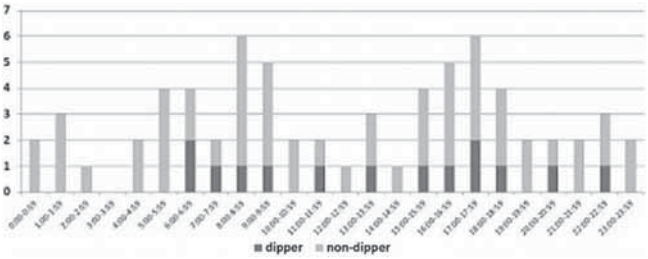

Figure 1. Circadian variation of aortic dissection.

Conclusions: Non-dipper pattern of BP was frequently seen in AAD patients. Absence of nocturnal BP fall may be a risk factor of AAD. Circadian variation of BP may also affect the onset time of type B AAD.

P6140 | BEDSIDE
The prevalence and related risk factors of prehypertension in middle age and elderly population with impaired fasting glucose

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Both prehypertension and impaired fasting glucose (IFG) have been strongly associated with cardiovascular disease. But there have been few studies of the epidemiology and risk factors of prehypertension with IFG. By analyzing cross-sectional cohort data from total 824 individuals aged 45 or over (men 343, women 481) who live in our city, we evaluated the prevalence and risk factors of prehypertension with IFG among local residents. The prehypertension was defined as systolic blood pressure is from 120 to 139 mmHg, and/or diastolic blood pressure is from 80 to 89 mmHg. The IFG was defined as fasting serum glucose concentration is from 100 to 125 mg/dl. The prevalence of prehypertension with IFG was 7.8% (64 of total 824, men 24, women 40). The prevalence of normotension with normoglycemia was 10.4% (85 of total 824, men 27, women 58). An univariate analysis showed body mass index, waist circumference, gamma-glutamyltransferase, total cholesterol, triglyceride, insulin, homeostasis model assessment of insulin resistance (HOMA-IR) were significantly higher in prehypertension with IFG group than normotension with normoglycemia group. Whereas adiponectin was lower than normal group. A multivariate analysis showed body mass index (BMI), serum triglyceride (TG) concentration and HOMA-IR were significantly associated with coexisting prehypertension with IFG group (BMI≥23 kg/m^2 odd ratio odd ratio 2.579, 95% confidence interval 1.026 - 6.487. p-value 0.044, TG≥150mg/dL odd ratio 7.313, 95% confidence interval 2.272-23.541. p-value 0.001, HOMA-IR≥1.5 odd ratio 11.242, 95% confidence interval 2.543-49.696. p-value 0.001). These data suggested that the prevalence of prehypertension with IFG was 7.8% and related risk factor is body mass index, triglyceride and HOMA-IR. BMI is independent risk factor if BMI is over 23 kg/m^2, high serum triglyceride concentration (TG≥150mg/dL) and HOMA≥1.5 was independent risk factor of prehypertension with IFG among local residents men aged 45 or over in our city.

P6141 | BEDSIDE
Association between office blood pressure and self-reported apneas in epidemiology study

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Objective: To evaluate association between anthropometric parameters, office blood pressure (BP) and self-reported sleep apneas in a randomized cohort from Russian epidemiologic study (ESSE-RF).
Design and methods: A randomized sample included 1600 St Petersburg citizens aged 25-65 years, 1597 subjects [mean age 50 (21-68), males – 570 (35.7%)] were eligible for analysis. All participants underwent a survey, including questions on sleep duration; BP was measured according to European guidelines on diagnostics and management of arterial hypertension.
Results: According to the survey data 939 subjects (338 males and 601 females) did not complain on sleep apneas, 83 participants (39 males and 44 females) complained on sleep apneas, and 575 subjects (193 males and 382 females) could not give any definite answer ($\chi 2=5.79$; $p=0.055$). Snoring subjects were older compared to non-snoring respondents and those who could not give a definite response [54 (26-65); 48 (25-68) and 52 (21-66) years, respectively; $F=17.9$; $p<0.001$]. Snorers were also more obese: body mass index (BMI) 28.5 (18.8-43.6); 25.9 (15-65) and 27.9 (16.3-51.7) kg/m^2, respectively ($F=126.5$; $p<0.001$), and the median waist circumference (WC) was higher in both males [100.5 (81-122); 93 (64-140.5) and 96 (66.5-133) cm, respectively; $F=9$; $p<0.001$] and females [91 (62-123); 83.4 (44-126) and 89.5 (57-139) cm, respectively; $F=19$; $p<0.001$] indicating android obesity. One-way analysis of variance showed higher office systolic BP [32.5 (90-180); 124 (85-225) and 130 (90-240) mmHg, respectively; $F=12.6$; $p<0.001$] and diastolic BP [82 (67-107); 78.5 (48-131) and 80 (51-150) mmHg, $F=7.8$; $p<0.001$] in snorers compared to non-snorers and participants who did not give a definite answer about snore. After adjustment for BMI and WC the differences in systolic ($F=103.4$; $p<0.001$), and diastolic ($F=95.2$; $p<0.001$) BP were still significant.
Conclusion: Epidemiologic data confirm that prevalence of sleep apneas increases with age. Subjects with self-reported sleep apneas are characterized by higher BMI, mostly due to the abdominal fat. Both systolic and diastolic BP is higher in respondents with self-reported sleep apneas independently of the major risk factors, including age, BMI and WC.

P6142 | BEDSIDE

Age-dependent blood pressure increase in different brazilian race/ethnic groups

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Background: Arterial pressure (AP) depends on interaction between genetic and environmental factors. Population-based studies show higher AP levels in African ancestry subjects. It is still controversial if this finding depends on genetic or on environmental/social factors. Age-related AP increase in different race/ethnic groups was investigated.
Methods: ELSA-Brasil is a cohort (35-74 y; N=15,105) to investigate determinants of chronic diseases. In baseline exams three AP readings were obtained (Onrom 765CP) in fasting conditions. Race/ethncity (white, black, indigenous, asian or "brown") was self reported. "Browns" are mixed subjects with a recognized African ancestry. Linear regression was used to calculate age-related systolic and diastolic AP increase.
Results: Analysis included individuals of the three groups (white, black and brown) not in use of antihypertensive drugs. Significant ($p<0.001$) regression was observed in all groups for both genders. In men, systolic AP increase (mmHg) per decade was 3.0 in whites, 4.5 in browns and 5.4 in blacks ($p<0.001$). In women these values were, respectively, 4.9, 6.4 and 6.4 mmHg/decade ($p<0.001$). Differences among groups remained significant after adjustment for age, body mass index (BMI) and socioeconomic variables (education, income and work activity.

Arterial pressure and race/ethnicity

	Men			Women		
	White	"Brown"	Black	White	"Brown"	Black
N	2582	1488	611	3268	1553	883
Age (years)	50.8±9,1	76.8±8.1	78.6±8.2	50.7±8.6	49.7±8.0	49.2±7.9
BMI (kg/m^2)	26.3±4.1	26.1±4.0	26.5±3.9	25.9±4.7	26.5±4.5	27.4±5.1
SBPcr	121.2±14.1	124.5±15.4	128.4±16.9	112.3±13.7	115.1±14.9	118.3±15.8
SBPadj	122.5±4.9	123.6±5.0	125.0±4.7	113.5±5.4	114.4±5.5	115.1±5.5
DBPcr	76.9±9.9	78.9±10.5	80.9±10.9	71.4±9.1	73.4±9,6	75.2±10.7
DBPadj	77.6±3.3	78.4±3.25	79.2±2.9	72.1±3.0	72.9±3.2	73.6±3.2

Crude (cr) and adjusted (adj) systolic and diastolic blood pressure (mmHg). Value are mean±sd. N=number of individuals.

Conclusion: In absence of the influence of antihypertensive drugs, Blacks shows higher AP values as compared to whites and this difference cannot be explained by socioeconomic variables in the Brazilian population.
Funding: Brazilian Ministries of Health and Science & Technology, FINEP and CNPq.

CARDIOMYOPATHIES I

P6144 | BEDSIDE

Clinical characteristics and cardiac magnetic resonance for the patients received repeat percutaneous transluminal septal myocardial ablation in refractory hypertrophic obstructive cardiomyopathy

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Background: Percutaneous transluminal septal myocardial ablation (PTSMA) is a promising alternative to surgical myectomy, however, there are problems regarding the residual gradient and repeat septal reduction therapy. Therefore, we investigated the clinical characteristics and the morphological analysis of cardiac magnetic resonance (CMR) in the patients received to repeat PTSMA.
Methods: We performed PTSMA procedures for 157 patients from 1998 to 2013, and 30 patients received repeat procedure (Group R) because of residual gradient with refractory symptoms. We investigated the details of the baseline characteristics and the PTSMA procedures, and the morphological analysis of CMR (n=101), with comparisons between the patients in Group R (n=30) and those without repeat PTSMA (Group S, n=127).
Results: The interval of both PTSMA procedures was 616±501 days, and 16 patients (53%) received 2nd procedure within 1 years. In comparisons with Group S, the patients in Group R were younger (54±16 vs 64±13 years, $p<0.001$), lower in peak CPK (869±366 vs 1271±541U/L, $p<0.001$), higher in post-procedural gradient (36±40 vs 24±32 mmHg, p=0.038) and similar in baseline gradient (91 vs 83 mmHg, p=0.459), injected ethanol dosage (2.2±1.0 vs 2.6±1.3, p=0.158) and baseline NYHA functional class (2.7±0.3 vs 2.7±0.5, p=0.832). From CMR analysis, the left ventricular mass (187±56 vs 174±58 g, p=0.372), the left atrial diameter (44±7 vs 42±9mm, p=0.401), the number of regional hypertrophied segment in the left ventricle (4.2±3.2 vs 3.7±2.6 segments, p=0.670) and the delayed enhancement (4.8±4.2 vs 6.8±10.7 g, p=0.787) were similar in both groups. In multiple logistic regression model for the baseline characteristics, age (adjusted hazard ratio 0.562 [95%CI 0.404-0.782] per 10 years, $p<0.001$), peak CPK (adjusted hazard ratio 0.772 [95%CI 0.668-0.890] per 100 U/l, $p<0.001$) and post-procedural gradient (adjusted hazard ratio 1.152 [95%CI 1.020-1.301] per 10 mmHg, p=0.023) were significant predictors.
Conclusions: Age, post-procedural gradient and peak CPK of 1st PTSMA were independent variables to predict repeat procedure. It is reasonable to perform PTSMA for older patients, and sufficient ablation of the culprit septal myocardium is desirable to achieve favorable results.

P6145 | BEDSIDE

Cardiovascular impact of acquired familial amyloid polyneuropathy after sequential liver transplantation

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Purpose: Sequential liver transplantation (SLT), in which the liver of a patient with familial amyloid polyneuropathy (FAP) is transplanted into another patient, is a strategy that has been used to overcome the paucity of available organs. However, the long-term consequences of SLT, concerning the manifestations of acquired FAP and, in particular, its cardiovascular (CV) repercussions, have been under-addressed. Our purpose was to evaluate patients with acquired FAP (AFAP) after SLT and to study the occurrence of CV changes.
Methods: We studied 37 liver recipients whose donor was a FAP patient (with AFAP) and 664 subjects with an hereditary FAP-related transthyretin mutation (99% with TTR Val30Met mutation).
Results: Concerning AFAP, patients had a mean age at SLT of 53±7 years old and 70% were male. The median follow-up was 9 years (IQR 8-10) and, during that time, 54% of the recipients developed symptoms of AFAP.
The mean interval of time between SLT and clinical manifestations of AFAP was 7,4±3 years. However, given that amongst TTR carriers the beginning of symptoms was at 33 years old (IQR 28-32), with a minimum age of 20 years old, one would expect that the clinical manifestations of AFAP would appear only 2 decades after SLT. The first symptoms of AFAP were neurological in 85% of the cases, gastrointestinal in 7,5% and CV in 7,5%.
During follow-up, 22% of the patients developed CV symptoms (mean interval of 7,5±0,7 years after SLT). In this group, 4 patients had pacemaker, placed prophylactically before liver re-transplantation; the % of pacing was identical to other patients with FAP and none was pace-dependent. During follow-up, none of the patients died; 2 patients were re-transplanted and 2 are on the waiting list.
The prevalence of electrocardiographic changes, namely conduction disturbances, was not statistically different between AFAP and FAP, but the mean time of follow-up after the first clinical manifestations of AFAP was only 1 year (vs 5 years in FAP patients).
Conclusions: In our cohort, a significant proportion of SLT recipients developed symptoms in the first 8 years after transplantation - earlier than expected.
Even thought 1/5 of the SLT recipients reported CV symptoms, they didn't have major CV changes, but the follow-up time since the first clinical manifestations of the disease was quite short.
More studies are needed for an accurate evaluation of the incidence of clinical AFAP and for determining the natural history of patients after SLT, who seem to undergo a fastest progression of the disease, comparing to hereditary FAP.

P6146 | BEDSIDE

Prognostic significance and impact of left-sided valvular thickening in patients with systemic light-chain amyloidosis

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Background: Left-sided valvular thickening (LVT) have been described in patients with systemic light-chain amyloidosis (AL) reflecting probable heavy infiltration of the valvular endocardium by amyloid proteins. However, the exact prevalence at initial diagnosis and the prognostic significance of LVT-AL have never been investigated in large series of AL-patients.
Methods and results: Comprehensive transthoracic echocardiography was performed in 150 patients with confirmed AL (mean age 68±11 years; 59% of male). The presence of mitral and/or aortic valve thickening was assessed visually. Overall, 42% had LVT-AL at baseline. Compared to patients without LVT-AL, those with LVT-AL were significantly older (p=0.008), with more frequently advanced NYHA functional class (p=0.007). They also had higher left ventricular (LV) wall thickening and mass, left atrial size, mitral E/E' ratio and systolic pulmonary artery pressures and lower LV ejection fraction, and both peak mitral and tricuspid S'-wave velocity (all $p<0.01$). Patients with advanced Mayo Clinic stage more frequently had LVT-AL: 58% in stage III vs. 45% in stage II and 5% in stage I, $p<0.0001$. In addition, patients with severe symptoms more frequently exhibited LVT-AL (63% in NYHA III-IV vs. 33% in NYHA I-II, p=0.0008).
During the follow-up, 79 deaths occurred with a higher rate of death in LVT-AL group than in no LVT-AL group (68% vs. 41%, p=0.001). The presence of LVT-AL was significantly associated with reduced 5-year survival: 32±7% vs. 64±6% in

no LVT-AL group (figure). In multivariable analysis, even after adjusting for age, gender, NYHA functional class and LV ejection fraction, LVT-AL remains a significant marker of mortality (Hazard ratio= 1.9, 95%CI: 1.1-3.2, p=0.02).
Conclusion: The presence of LVT-AL is a common finding in patients with AL and is associated with impaired both LV systolic and diastolic function, worse functional status and advanced stage of the disease. In addition, LVT-AL is a powerful marker of mortality. These results suggest that the assessment of LVT-AL may help to enhance risk stratification of AL patients.

P6147 | BENCH
Unequal abundance of mutated myosin among individual cardiomyocytes: the trigger for myocardial phenotype development in familial hypertrophic cardiomyopathy related to beta-myosin mutations?

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Familial Hypertrophic Cardiomyopathy (FHC) is the most common inherited disease of the heart. In most cases it is caused by mutations in sarcomeric proteins. About 1/3 of the patients are heterozygous for missense mutations in the ß-myosin heavy chain (ß-MyHC). It is generally assumed that pathological hypertrophy, myocyte disarray and other features result from functional changes induced by the respective mutation at the sarcomeric level. Yet, the underlying pathomechanisms are still unclear. Different mutations even in the same protein affect function of the sarcomere quite differently and a common trigger for development of the FHC-phenotype has not yet been identified.
In earlier work on muscle fibers we found large functional variation, and large variation in mutated ß-MyHC-mRNA expression among individual slow fibers of the soleus muscle of affected FHC-patients in which the ß-cardiac MyHC is the expressed MyHC isoform. We concluded that the observed functional variation results from variation in the expression of mutated ß-MyHC from fiber to fiber.
On this basis we hypothesized that FHC-typical myocardial features arise from variation in the expression of mutated myosin from cardiomyocyte to cardiomyocyte. Functional alterations caused by the mutated myosin such as higher force generation that we previously found for several FHC-related ß-MyHC-mutations would then lead to imbalanced force generation among neighboring cardiomyocytes, resulting in distortions and even disarray within the cellular network of FHC-patient's myocardium.
To test this hypothesis we quantified the relative abundance of mutated ß-MyHC-mRNA in individual cardiomyocytes isolated from cardiac samples of two FHC-patients with ß-myosin mutation R723G. We found that the relative expression of ß-MyHC-mRNA with the R723G mutation varies from cell to cell from almost pure mutant to almost pure wildtype expression. Measurements of force generation and calcium sensitivity of individual myocytes with the R723G mutation also revealed significantly larger functional variation compared to control myocytes.
Based on these data we propose that unequal expression of mutated ß-MyHC from cardiomyocyte to cardiomyocyte in FHC-patient's myocardium triggers functional imbalance, thus setting off altered cell signaling and morphology resulting in hypertrophy and myocyte disarray.

P6148 | BEDSIDE
Significance of ventricular wall thickening for assessing inflammatory activity in cardiac sarcoidosis

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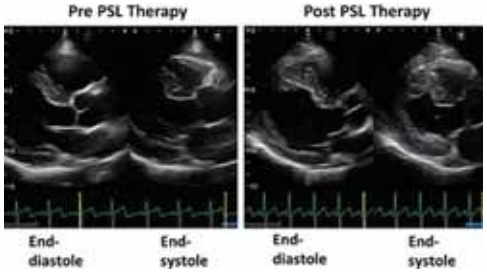
Purpose: Conventional echocardiography has an established role in assessing the morphological and functional status in cardiac sarcoidosis (CS), but its usefulness to evaluate the inflammatory activity in CS has not been determined.
Methods and results: 67-Gallium (Ga) single-photon emission computed tomography with integrated computed tomography (SPECT/CT) demonstrated that abnormal Ga uptake in the myocardium was observed in 15/27 consecutive CS patients. Each left ventricle was divided into four segments for evaluation, and 32/60 inflammatory segments detected by SPECT/CT corresponded with some echocardiographic abnormalities, such as abnormal wall motion (AWM), wall thickening (WT), and wall thinning. SPECT/CT sensitivity was 91% and the specificity was 52%. AWM was the most frequent observation (42/60 segments), although its specificity for myocardial inflammation was not high (56%). However, WT was less frequent (16/60 segments, 8 cases), and 15 segments corresponded to abnormal Ga uptake (specificity: 96%; positive predictive value: 94%). After 1 year of prednisolone (PSL) therapy, ameliorated WT associated with improvement of wall motion in 4/5 cases (Figure) and disappearance of Ga uptake in all cases was observed.
Conclusions: Echocardiographic abnormalities of WT coinciding with AWM may be highly specific not only for detecting de novo inflammatory regions but also for predicting of the reversibility of cardiac function, which aids in assessing the myocardium during long-term follow-up in patients with CS.



A case with wall thickening.

P6149 | BEDSIDE
Carpal tunnel syndrome in amyloidosis: prevalence, risk factors and correlation with cardiac involvement in a large cohort of 435 consecutive patients

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Purpose: Carpal tunnel syndrome (CTS) is one of the most common clinical manifestations of TTR-related amyloidosis, both hereditary (ATTR), and wild type (senile systemic amyloidosis, SSA) and often precedes cardiac symptoms. The exact prevalence of CTS in amyloidosis however is not known. We therefore aimed to establish prevalence, risk factors and possible association with cardiac involvement in patients with TTR-related and AL amyloidosis.
Methods: We retrospectively analyzed clinical and instrumental (ECG and echocardiographic) findings of 260 patients with TTR-related and 175 with AL amyloidosis evaluated at our Centre between 1990 and September 2013.
Results: Prevalence was 35% in TTR-related amyloidosis (35% in ATTR and 32% in SSA) and 8% in patients with AL ($p<0.001$). Among TTR patients, CTS was more frequently associated with cardiac involvement (76% vs. 42%; $p<0.0001$) as reflected in the ECG and echo findings (Table 1), and manifested 9 years before the onset of cardiac symptoms. Among patients with cardiomyopathy with/without CTS there were no significant clinical/instrumental differences. At univariate analysis male gender and genotype were not associated with CTS.

ECG/echo findings in TTR amyloidosis

	ATTR			Wild type		
	CTS (72)	No CTS (132)	p	CTS (18)	No CTS (38)	p
Men, n (%)	37 (51)	76 (58)	0.483	16 (89)	32 (84)	0.953
Cardiomyopathy, n (%)	55 (76)	55 (42)	<0.0001	n.a.	n.a	n.a.
Total QRS score (mV)	107 [88–128]	118 [96–139]	0.044	127 [113–150]	116 [97–143]	0.170
Presence of infarct pattern, n (%)	37 (51)	30 (23)	<0.0001	13 (72)	24 (63)	0.714
Mean LV wall thickness (mm)	16 [12–18]	11 [10–15]	<0.0001	18 [16–19]	16 [14–18]	0.06
Left atrial diameter (mm)	44 [40–46]	39 [34–48]	0.001	51 [46–57]	46 [43–51]	0.03
Pericardial effusion, n (%)	27 (38)	28 (21)	0.019	10 (56)	21 (55)	0.789

Conclusions: CTS is specifically associated with TTR-related amyloidosis (but not AL) independently from patient gender. In TTR-related amyloidosis, CTS is more frequently associated with cardiac involvement, even though patients with cardiomyopathy with/without CTS have a comparable clinical/instrumental profile. CTS precedes cardiac symptom onset by 9 years, this finding is important for an early diagnosis of amyloidotic cardiomyopathy.

P6150 | BEDSIDE
Natural evolution of cardiomyopathy in Friedreich's ataxia

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Friedreich ataxia (FA) is the most common autosomal recessive cerebellar ataxia, due to a GAA expansion in the frataxin gene. FA is associated with a hypertrophic cardiopathy, heart failure is a frequent cause of death. Little is known about the long term evolution of the cardiopathy.
We included genetically confirmed FA patients if they had normal LVejection fraction and at least 2 evaluations with 1 year interval. News were obtained from all patients. We performed 517 cardiac evaluations (clinical examination, ECG, echocardiography).
We studied 109 patients (mean±SD,29±10y), 58% female. At inclusion: age at onset of the disease was 15±7y, disease duration was 15±8y, 86 were wheelchair users, the age of wheelchair onset was 25±9y, and mean smaller GAA expansion was 1.91±0.7Kb.
We defined 3 groups according to the cardiac hypertrophy: no, mild and severe. Characteristics of the patients at inclusion are in the table.

Characteristics of patients

	No hypertrophy (n=13)	Mild hypertrophy (n=29)	Severe hypertrophy (n=67)
Age, y	35±10	32±11	27±8
Age at onset,y	18±9	17±10	13±5
Wheelchair user	7	22	57
Age at wheelchair onset, y	33±9	29±12	23±7
smallerGAA,Kb	1.70±0.69	1.72±0.81	2.0±0.65
IVS,mm	8.5±0.8	10.4±1.1	13.2±2.4
PW,mm	8.3±0.9	9.5±1.2	12.5±2.1
LVEDD,mm	44±5	44±4	41±4
LVESD,mm	26±5	26±5	24±5
LVEF, %	66±5	67±8	69±7

IVS, interventricular septum; PW, posterior wall; LVEDD, LV end diastolic diameter; LVESD, LV end systolic diameter; LVEF, LV ejection fraction.

During a mean follow-up of 12±5y: 23 patients experienced at least one of the following events: atrial fibrillation (n=19), heart failure (n=12), LV dysfunction LVEF <50% (n=13), stroke or cardiac embol (4); 1 heart transplantation and 13 deaths occurred. The death was from cardiac origin (heart failure or stroke) in 8, from respiratory origin in 1. The cause of death was unknown in 4 patients.
Patients with no hypertrophy had a better prognosis than the others with 100% survival (G1) vs 91% (G2) and 80% (G3). Majority of the events occurred in patients with severe hypertrophy.

P6151 | BEDSIDE
Myocarditis is a marker of active disease in arrhythmogenic cardiomyopathy: clinical features and outcomes in a spanish cohort

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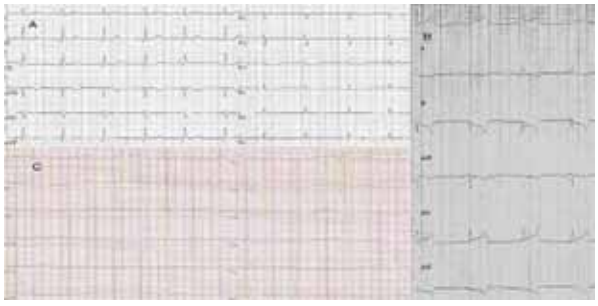
Introduction: Myocarditis and arrhythmogenic cardiomyopathy (ACM) are entities intimally related. "Myocarditis-like" episodes seem to be a marker of active ACM. We aimed to evaluate the clinical features of this these so- called active or "hot phases" and whether they are associated with a poor prognosis or a high risk of malignant arrhythmias.
Methods: We evaluated 164 ACM patients (81 arrhythmogenic right ventricular cardiomyopathy, 65%males, mean age 45 years old and 83 left side forms of ACM, 49% males, mean 43 years old). We also evaluated 54 non affected carriers of mutations associated with ACM (37% males, mean 40 years old). Blood tests (hemogram, leucocyte formula, CRP and troponin I), ECG and imaging test performed at the time of the myocarditis were reviewed.
Results: We identified 6 patients that presented with a clinical diagnosis of acute myocarditis during the follow-up (median 34 months).Myocarditis preceded a worsening in systolic function in 2 patients. It was associated with an increase in the gadolinium pattern in 1 case. New repolarization abnormalities appeared in 2 patients. Chest pains preceded the development of ventricular tachycardia in 1 case. Only 1 healthy mutation carrier did not suffer any change in her condition. Myocarditis was the first clinical presentation of ACM in 5 out of 6 cases.



ECG before, during and after myocarditis

Conclusion: Myocarditis may be the first clinical presentation of ACM. It reflects an active phase of the disease and it is associated with progression and changes in the phenotype, ranging from isolated ECG changes to worsening in the systolic function or ventricular arrhythmias.The diagnosis ACM should be suspected in the event of recurrent myocarditis or myocarditis associated with family history of ACM.

P6152 | BEDSIDE
Soluble ST2 is associated with reduced myocardial function and arrhythmic events in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC)

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Purpose: Risk stratification for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy (ARVC) remains challenging. Soluble ST2 (sST2), a member of the interleukin 1 cytokine family, can be induced in mechanically overloaded cardiomyocytes and is elevated in patients with left ventricular (LV) heart failure. In ARVC patients, right ventricular (RV) function is predominantly affected. We wanted to explore if the plasma concentration of sST2 was associated with reduced myocardial function and arrhythmic events in patients with ARVC.
Methods: We included patients with ARVC and their mutation positive family members. sST2 was determined by ELISA in plasma collected at time of echocardiographic examination. Myocardial function was assessed by echocardiography including strain by speckle tracking technique. RV function was assessed by RV fractional area change (FAC) and by RV global strain (average longitudinal strain from 6 RV segments). LV function was assessed by ejection fraction (LVEF) and LV global strain (average longitudinal strain in 16 LV segments).
Results: We included 46 ARVC mutation positive subjects (age 41±15 years, 21 female), of whom 22 had previous ventricular arrhythmia and 24 had no arrhythmic events. sST2 was elevated in those with arrhythmias compared to those without (34±13 ng/mL vs. 26±7 ng/mL, p=0.009). sST2 correlated with RV function by RV global strain (R=0.51, p=0.001) and RVFAC (R=0.36, p=0.02) and with LV function by LVEF (R=-0.43, p=0.003) and LV global strain (R=0.48, p=0.001). ROC analyses for sST2 showed C-statistics of 0.70; 95% CI 0.55-0.86. A sST2 level of 30 ng/mL identified ARVC patients with ventricular arrhythmias with a sensitivity of 50% and a specificity of 88%.
Conclusions: Soluble ST2 was elevated in ARVC patients with arrhythmic events and correlated well with RV and LV function. sST2 may be of additive value in risk stratification for ventricular arrhythmias in ARVC.

P6153 | BENCH
End-stage hypertrophic cardiomyopathy phenotype is an age-specific red flag for aetiological diagnosis

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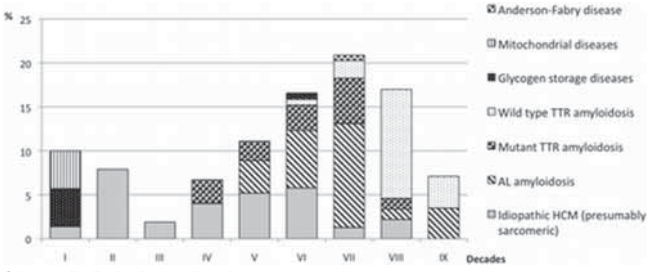
Purpose: Left ventricular (LV) hypokinesia associated with hypertrophic cardiomyopathy (HCM) phenotype (end-stage evolution) includes a broad spectrum of disease subtypes and carries an ominous prognosis due to high rates of refractory heart failure and sudden arrhythmic death. The prevalence of the different aetiologies in adults and children is not known. Additionally, the age-distribution of the different disease subtypes of the end-stage HCM phenotype have not been evaluated.
Methods: A total of 103 patients with LV hypokinesia (ejection fraction <50%) associated with HCM phenotype (0-89 years) were evaluated at our referral center between 1990 and 2013. Aetiological diagnosis was made on the basis of clinical/instrumental features with particular attention to the presence of multi-organ involvement, type of inheritance, molecular biology, specific metabolic exams, cardiac or skeletal muscle biopsy, magnetic resonance imaging and 99mTc-DPD scintigraphy.
Results: According to the age at diagnosis, 93 patients (90%) were adults and 10 (10%) children (of whom 6% infants). The prevalence of the different disease aetiologies was: 66% amyloidosis (18% transtiretin-related, 15% wild type and 33% amyloid light chain), 26% sarcomeric HCM, 4% glycogen store diseases, 3% mitochondrial diseases and 1% Anderson-Fabry disease. The distribution of the different aetiologies according to age decades is presented in the figure. A strong relation between age at diagnosis and disease subtype was present, indicating that the finding of the end-stage HCM phenotype can suggest a specific diagnosis according to the age at presentation.



Subtype distribution by age decade.

Conclusions: LV hypokinesia associated with HCM phenotype (end-stage evolution) can be considered an age-specific red flag for the disease subtype.

P6154 | BEDSIDE

Serial apical deformation change is predictive of outcome in patients with cardiac amyloidosis

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Purpose: Apical sparing pattern with preserved longitudinal systolic strain (LSsys) at apical segments and significantly reduced LSsys at mid and basal segments is a typical finding in patients with cardiac amyloidosis (CA). Reduced mid-septal LSsys is associated with poor outcome in CA patients. The purpose of this prospective study was to explore the predicting value of monitoring regional LSsys on outcome in CA patients.
Methods: Standard echocardiography was performed in 38 biopsy proven CA patients (mean age 65±10 years; 55% male) at baseline and during echocardiographic follow-up (median 278 days). Global and segmental LSsys were offline assessed by two-dimensional speckle tracking imaging in septal and lateral walls of left ventricle (LV) from apical 4-chamber view. All patients were clinically followed-up by clinical visit or telephone call (median 486 days). The primary endpoint was defined as all-cause death.
Results: Twenty out of 38 (53%) patients died during clinical follow-up. During follow up, NYHA class was significantly increased in non-survivors while remained unchanged in survivors, LV wall thickness and right ventricular dimension were significantly increased in both non-survivors and survivors (all $P<0.05$), LV global and regional LSsys remained unchanged in survivors while septal and lateral LSsys at apical segments were significantly reduced in non-survivors (septal: -18±6% vs. 15±7%, P=0.022; lateral: -16±7 vs. 12±6, P=0.006). Univariate Cox analysis showed that baseline NYHA class (HR 2.75, P=0.034), LV mass index (HR 2.97, P=0.042), mid-septal LSsys, (HR 2.82, P=0.028), LSsys reduction of apical-septal (HR 3.34, P=0.016) and apical-lateral (HR 5.61, P=0.001) segments during follow-up were predictors of mortality. Apical-septal and apical-lateral LSsys remained independent mortality predictors after adjustment for age, gender, baseline NYHA class, LV mass index, and LV ejection fraction. CA patients with apical-septal LSsys reduction >2.5% or apical-lateral LSsys reduction >3.0% during follow-up was associated with a 4-5 fold higher risk of death compared to those with apical-septal LSsys reduction ≤2.5% or apical-lateral LSsys reduction ≤3.0%.
Conclusion: Longitudinal systolic strain reduction at apical segments over the follow-up period is an independent predictor of survival in CA patients.

P6155 | BEDSIDE

Clinical and genetic predictors of major cardiac events in patients with Anderson-Fabry disease

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Purpose: To determine the incidence of major cardiac events and to identify clinical and genetic predictors of adverse cardiac outcomes in patients with Anderson Fabry Disease (AFD).
Methods: An observational, longitudinal, retrospective evaluation of 207 consecutive patients was performed. Missense mutations in exon 1 (Ala20Pro), exon 5 (Ans215Ser) and exon 6 (Met296Val, Met296Ile, Gln279Glu and Arg301Gln) of the α-galactosidase A gene were coded as cardiac variants. All other mutations were considered "classical" mutations. The primary end point was a composite of the following events: Severe heart failure symptoms (NYHA III/IV), atrial fibrillation, bradycardia requiring device insertion and cardiac death. The influence of age, gender, MSSI, LA diameter, EF, indexed LV mass, PR interval, QRS duration and cardiac variant on outcomes was examined.
Results: 30 individuals reached the primary end-point (6 had cardiac variants). The incidence of the primary endpoint was 2.64 per 100 person-years (CI 1.78–3.77). The multivariable predictors for the primary endpoint and individual outcomes are shown in the table.

Multivariable predictors of outcomes

Dependent variable	Independent variable	Exp(B)	CI	p
NYHA III/IV	Age	1.052	1.010–1.095	0.015
	Indexed LV mass	1.010	0.999–1.021	0.081
AF	Mutation	0.49	0.004–0.633	0.021
	Age	1.107	1.018–1.204	0.017
	Indexed LV mass	1.027	1.014–1.040	<0.001
PPM	Age	1.052	0.999–1.108	0.056
	MSSI	1.074	1.010–1.143	0.024
	QRSd	1.044	1.011–1.078	0.009
Death	EF	0.835	0.747–0.934	0.002
	Indexed LV mass	1.037	1.018–1.056	<0.001
Composite	Age	1.047	1.014–1.081	0.005
	MSSI	1.053	1.013–1.094	0.009
	QRSd	1.027	1.005–1.051	0.018

Conclusions: AFD is associated with a high burden of cardiac morbidity and mortality. This is associated with increasing age, global severity of AFD and QRS duration. Outcomes are similar in patients with and without cardiac genetic variants.

CARDIOMYOPATHIES II

P6157 | BEDSIDE

Prognostic value of changes in blood pressure profile in patients with familial amyloid polyneuropathy

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Background: Changes in blood pressure (BP) profile including abnormality in the circadian variation are frequent in patients with familial amyloid polyneuropathy (FAP) V30M-TTR and are attributed to autonomic dysfunction. However these changes have never been well characterized and its prognostic value is unknown.
Purpose: To evaluate the influence of age and duration of symptoms on the BP profile and determine the impact of BP changes in the prognosis of patients with FAP.
Methods: V30M-TTR mutation carriers underwent annual cardiac evaluation which included ambulatory blood pressure monitoring (ABPM). Hypertension was defined as daytime BP ≥140/90 mmHg or nighttime BP ≥125/75 mm Hg. The non-dipper pattern was defined as a decrease in systolic BP at night <10% and the reverse dipper pattern as systolic BP higher at night.
Results: 226 patients (45±14 years, 54.4% female) were enrolled. During a follow-up of a median of 50 months, 756 exams were performed. Hypertension was documented in 37.1% of the exams (N=279) increasing its occurrence with age (23.8% in patients aged <30 years vs. 67.3% in those aged >70 years; $P<0.001$) and with the duration of symptoms (37.1% in patients with symptom duration <2 years vs. 54.1% in those with evolution >9 years; P=0.006). The 24 hr systolic BP increased progressively with age (Pearson R 0.21, $P<0.001$) but not with the duration of symptoms. On the contrary, the 24 hr diastolic BP increased with duration of symptoms (Pearson R=0.13, P=0.004) but not with age. During follow-up, 36 patients (15.9%) died. Multivariate Cox regression analysis (backward conditional method) with adjustment for age, showed that the risk of death increased with nocturnal systolic loads [Hazard Ratio (HR)=1.03, 95% CI 1.02-1.05; $P<0.001$] and with nocturnal decline in systolic BP (HR: 1.07, 95% CI 1.03-1.12; P=0.001). On the other hand the risk decreased with the 24 hr systolic BP (HR: 0.94, 95% CI 0.91-0.97; $P<0.001$) and diastolic daytime loads (HR: 0.98, 95% CI 0.96 to 0.995; P=0.013). Among the patterns of circadian BP variation, the one with the greatest prognostic impact was the reverse dipper with more than twice the risk of death (HR: 2.62, 95% CI 1.54 to 4.45; $P<0.001$).
Conclusions: In patients with FAP, the changes in the BP profile are associated with the risk of death. The ABPM is an inexpensive diagnostic method that can help to identify patients with unfavorable prognosis.

P6158 | BEDSIDE

Electrocardiographic QRS fragmentation as a marker for myocardial scarring in hypertrophic cardiomyopathy

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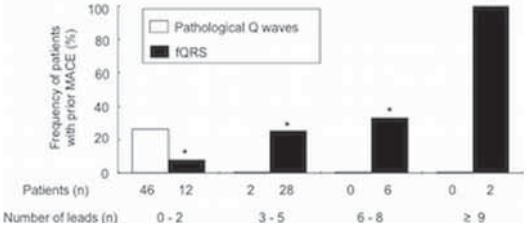
Background: Fragmented QRS complexes (fQRS) on a 12-lead ECG reflect intraventricular conduction delay and have been demonstrated to be a marker for myocardial scarring in coronary artery disease. However, few data exist regarding the diagnostic value of fQRS for estimating myocardial scarring in patients with hypertrophic cardiomyopathy (HCM).
Objective: We assessed whether fQRS shows better correlation with myocardial scarring than pathological Q waves in patients with HCM.
Methods and results: Forty-eight patients with HCM who underwent 12-lead ECG and cardiac magnetic resonance with late gadolinium enhancement (LGE-CMR) were investigated. The overall sensitivity, specificity, and accuracy of pathological Q waves were 9%, 95%, and 60%, respectively, for detecting myocardial scarring in the corresponding LV segments, and those of fQRS were 43%, 73%, and 61%, respectively. The number of leads displaying fQRS correlated with the extent of myocardial scarring (r=0.40, p=0.0047), whereas there was no correlation between the number of leads with pathological Q waves and the extent of



myocardial scarring. The frequency of prior major cardiovascular events (MACE) increased according to the number of leads with fQRS (p=0.019).
Conclusions: fQRS showed a substantially higher sensitivity compared with pathological Q waves for detecting myocardial scarring in HCM. Furthermore, the number of leads with fQRS was associated with both the extent of myocardial scarring and the frequency of prior MACE. Even with availability of CMR, the 12-lead ECG can be used as a screening modality for myocardial scarring in HCM because of its simplicity and cost-effectiveness.

P6159 | BEDSIDE
Arrhythmogenic right ventricular dysplasia - is it true diagnosis or hyperdiagnostic?

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One of the causes of the sudden cardiac death is arrhythmogenic right ventricular dysplasia (ARVD/C). The first symptom is ventricular arrhythmia (VA) in the most cases. From 2010 there is a new guideline of Marcus F.I. et al., for diagnosis of ARVD/C. It was actually to compare the sensitivity of various diagnostic schemes, and it was necessary to review the criteria of the disease in patients with VA.
The aim of the study was to compare the detection of ARVD/C rate according to criteria McKenna WJ et al., 1994 and Marcus FI et al., 2010.
Materials and methods: 369 patients with nonischemic frequent VA (175 m and 194 f, 45±25 years) were included in the study. We analyzed family history, ECG, echocardiography (EchoCG), Holter monitoring ECG (HM ECG), exercise training test (ETT), coronary angiography, MRI, in some cases EMB.
Initially, the diagnosis ARVD/C was established in 17 patients (5 m, 12 f, 40±20 years) - 4.6% of the total patient number. However, according to the criteria 2010, ARVD/C diagnosis was revised and established in 47 patients (15 m, 32 f, 40±25 years) - 12.74% of the total.
According to the criteria 2010 18 patients (38.3%) had 2 major criteria, 27 patients (57.4%) - 1 major and 2 minor criteria. In 2 patients (4.3%) we observed 4 minor criteria. Also we found a linear correlation between the findings on ECG and EchoCG (r= -0,096). Using new criteria we more often found ventricular extrasystoles (more than 500 beats per 24 hours) in 58.8% and 76.6% cases, the paroxysms of right ventricular tachycardia 52.9% and 59.6%, RV enlarging according to EchoCG d 27.7%, the presence of epsilon waves 11.7% and 6.3% and the diagnosis was coincided only in 17 patients (36%) of the total number of patients ARVD/C diagnosed using 2 different diagnostic schemes.
So we diagnosed ARVD/C in 36% more cases often by using the criteria 2010 than using the criteria 1994. Also we discovered an inverse and weak relationship between ECG and EchoCG datas, which is probably explained by the staging of the disease (early electrical phase before the appearance of structural changes). Also it is important to note that VT presence was discovered in the third of cases only during ETT which is not included in diagnostic criteria tests. We are following up these patients to understand if it is hyperdiagnostic criteria scheme or not.

P6160 | BEDSIDE
More impaired diastolic function of light chain amyloidosis contribute to poor prognosis compared with transthyretin amyloidosis: result from longitudinal study of biopsy-proven cardiac amyloidosis

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Background: Immunoglobulin light chain (AL) amyloidosis is associated with higher mortality than transthyretin (TTR) amyloidosis, however, few data exist regarding the relationship between difference of type of amyloidosis and cardiac mortality, especially in hemodynamic and echocardiographic parameters.
Methods: We reviewed 51 consecutive patients with biopsy-proven cardiac amyloidosis from 1993 to 2013. Of these, 27 were AL amyloidosis and 24 were TTR amyloidosis. Hemodynamic, echocardiographic and clinical parameters were assessed. Patients were retrospectively followed for cardiac mortality.
Results: There were no differences between AL and TTR in age (68±7 vs 70±10, p=0.14). Frequency of male was lower in AL than TTR (70 vs 92%, p<0.05). BNP level was higher in AL than in TTR (1129±267 vs. 377±76 pg/ml, p<0.05). In hemodynamic parameters, AL demonstrated lower cardiac output and higher left ventricular (LV) end-diastolic pressure than TTR, but not statistically significant (4.2±1.5 vs 4.7±1.0L/min, p=0.306 and 17.5±4.9 vs 14.0±8.3 mmHg, p=0.179, respectively). In echocardiographic parameters, LV ejection fraction, LV wall thickness, LV mass index, left atrial dimension and trans-mitral E/A ratio were comparable between the two groups. Interestingly, deceleration time of early filling was significantly shorter in AL than those of TTR (153.2±47.4 vs. 186.1±49.4ms, p<0.05). And AL was associated with smaller LV end-diastolic diameter and higher E/e' than those of TTR, however, not statistically significant (43.1±6.8 vs. 47.1±7.6mm, p=0.060 and 23.3±15.1 vs 20.8±7.1, p=0544, respectively). During mean follow-up period of 734 days, 20 patients died in AL and 6 in TTR (74 vs 25%, P<0.05). Kaplan-Meier curve analysis demonstrated that probability of free of cardiac death was significantly lower in AL than that of TTR (log-rank. p<0.05). Average survival time from diagnosis to death was 272.2±113.3 days in AL, 1675.1±745.4 days in TTR (P<0.05). Survival rate at 1 year from diagnosis was significantly lower in AL than in TTR (23 vs. 53%, p<0.05). In AL, 1-year nonsurvivors showed shorter deceleration time than those of survivors, however, not statistically significant (131±30 vs. 177±51ms, p=0.069).
Conclusions: AL amyloidosis showed more restrictive physiology compared with TTR amyloidosis which could cause impaired diastolic function and higher cardiac mortality. Furthermore, only in AL amyloidosis, more impaired diastolic function might account for poor prognosis.

P6161 | BENCH
Early detection of diastolic and systolic dysfunction with speckle-tracking echocardiography in carriers of hypertrophic cardiomyopathy mutations

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Purpose: Diastolic dysfunction has been described as the first abnormality in patients with sarcomeric mutations, prior to left ventricular hypertrophy (LVH). Previous studies have demonstrated that regional peak systolic longitudinal strain (ε) and strain rate (SSR) are reduced in overt hypertrophic cardiomyopathy (HCM). The aim of this study was to assess early changes in diastolic and systolic function using speckle tracking echocardiography in subjects with genotype positive-phenotype negative (G+/LVH-) HCM.
Methods: In this single-center prospective cohort of G+/LVH- patients, 78 (43% male, age 41±13 years) patients underwent ≥2 echocardiographic evaluations between 2006-2013. Structural characteristics, systolic function and diastolic function were assessed by 2D-echocardiography, and segmental longitudinal ε and SSR were measured from apical 4-, 2-, and 3-chamber views. One (1%) patient with undeterminable diastolic function was excluded. The standard diagnostic criteria for HCM were used.
Results: During a mean follow- up of 4.7±1.9 y (range 1.2-8.1 y), 1 patient developed overt HCM (LVH of 15 mm, after 6.6 y). No cardiac events occurred. Twelve (15%) patients had diastolic dysfunction at baseline, and 12 (15%) other patients developed diastolic dysfunction during follow-up. Septal ε (from 20.8% to 16.7%, p=0.06) and septal SSR (from 1.46 to 0.98, p=0.009) decreased during follow-up in this latter group, despite normal ejection fraction. Left ventricular (LV) wall thickness (12±2 mm) and LV mass (181±56 g) were increased in these patients compared with patients without diastolic dysfunction (10±2 mm, p=0.01 and 145±44 g, p=0.02).
Conclusion: Preclinical HCM patients, who developed diastolic dysfunction, not only had increased LV wall thickness and LV mass, but also regional systolic dysfunction, demonstrated by ε and SSR analysis. This impairment of regional systolic function may underlie the development of asymmetric hypertrophy.

P6162 | BEDSIDE
Mechanisms of taxanes-induced cardiac dysfunction: a 4D echocardiographic and genetic study

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Background: Use of taxanes in breast cancer is often limited by the development of cardiac dysfunction, leading to increase of morbidity and mortality. Therefore, better understanding of mechanisms of cardiac dysfunction induced by taxanes is essential. Our aim was to evaluate whether increased oxidative stress and arterial stiffness has a determinant role in the development of taxanes-induced cardiac dysfunction, and if this is related to a specific genetic polymorphism.
Methods: We studied prospectively 45 women with breast cancer (43±8 years), without known cardiac disease, and LVEF>50%, scheduled to be treated with taxanes, at baseline, and after the completion of treatment (cumulative dose of 540±150 g/m^2). 4D auto LV quantification echo was used to assess LV geometry, ejection fraction (EF), and systolic deformation: radial (RS), longitudinal (LS), and circumferential strain (CS), and area strain (AS). Arterial stiffness was assessed from β index; myocardial damage from troponin-I; oxidative stress from Carbonyl Concentration into the Plasma Proteins – CCPP; and genetic variation from a single nucleotide polymorphism of genotype rs28371759, rs2032582, and rs1056836.
Results: After the completion of chemotherapy, there was a reduction of EF, radial and longitudinal deformation, and area strain, whereas circumferential deformation remained unchanged. These changes were associated with an augmentation of the oxidative stress and an increase of the arterial stiffness (table). Changes in LV deformation (LS and AS) were inversely related to changes in oxidative stress

Changes from baseline to follow-up

Taxanes	EF (%)	RS (%)	LS (-%)	CS (-%)	AS (%)	CCPP (nmol/mg)	β index
Baseline	62±4	62±7	21±3	22±3	39±3	0.336±0.104	7.7±3
Final	55±3	50±10	17±4	20±4	31±4	0.500±0.100	10.2±3
P	0.0001	0.014	0.012	0.72	0.001	0.001	0.001

and arterial stiffness (r=-0.56 and r=-0.49, for LS; r=-0.63 and r=-0.54, for AS; all p<0.01). Furthermore, homozygote of genotype rs1056836 was directly related to the decrease of EF and LS (r=0.59 and r=0.64, p<0.05) after the completion of treatment. Troponin-I was not changed.
Conclusion: Increased oxidative stress and arterial stiffness, and not direct myocardial damage, may play an essential role in the development of taxanes-induced cardiac dysfunction, probably associated with a specific genetic variation.
Acknowledgements: Grant 112/2011.

P6163 | BEDSIDE
Does alcohol septal ablation for hypertrophic obstructive cardiomyopathy induce ventricular arrhythmias?

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Objective: The purpose of the present study was to determine the incidence of ventricular arrhythmias before and after ASA.
Background: In patients with hypertrophic obstructive cardiomyopathy (HOCM), gradient reduction by alcohol septal ablation (ASA) is an alternative treatment option to surgical myectomy. However, concerns exist about whether the induction of a myocardial scar during ASA may create a substrate for ventricular arrhythmias.
Methods: The study group consisted of 44 patients in whom ASA was performed for symptomatic, drug-refractory hypertrophic cardiomyopathy. Continuous rhythm monitoring was obtained by an implantable loop recorder (n=30) or a pacemaker (n=14). The occurrence of ventricular and supraventricular arrhythmias before and after ASA was noted.
Results: The ASA procedure was considered successful (resting gradient <30 mmHg, and provoked gradient <50 mmHg at 4 months echocardiographic assessment in combination with NYHA Class functional status ≤2) in 30 (68%) patients. Rhythm monitoring before ASA was available in 28 patients. The mean duration of rhythm monitoring after ASA was 3.5±2.8 years. Sustained VT/VF within 30 days after ASA occurred in three patients (7%), including 2 cases of VF during the procedure, while no VT/VF was observed before ASA (p=0.10). No sustained VT/VF was observed >30 days after ASA. No deaths occurred during follow up.
Conclusions: We conclude that the obstruction relief and improved NYHA class functional status provided by ASA are not offset by a high incidence of late occurring ventricular tachycardia or ventricular fibrillation.

P6164 | BEDSIDE
A founder mutation of the myosin binding protein-C gene in hypertrophic cardiomyopathy and adverse outcomes with compound heterozygosity

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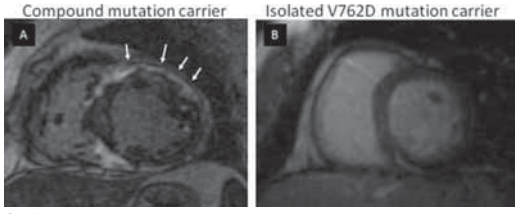
Purpose: Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, caused by sarcomeric genes mutations. Although most of founder mutation carriers that arose from a common ancestor exhibit favorable clinical phenotypes, there still remain small fractions of these carriers associated with increased cardiovascular events. However, few data exist regarding defining factors that modify phenotypes of these patients particularly in terms of multiple gene mutations. Therefore, we assessed genotype-phenotype correlations and investigated factors that contribute to phenotypic diversities of the founder mutation carriers.
Methods and results: We screened unrelated 488 probands with HCM for sarcomeric genes mutations. We identified a prevalent founder mutation (V762D) in the MYBPC3 in 33 subjects from 19 families. Among them, 28 carriers harbored isolated V762D mutation and exhibited a late onset of overt HCM than other MYBPC3 mutations carriers (62.8±3.0 years vs 50.1±2.6 years, p<0.05). In contrast, remaining 5 carriers had additional sarcomere-genes mutations (3 in the MYBPC3, 2 in the cardiac troponin T gene) and showed unfavorable phenotypes such as early disease onset and massive left ventricular fibrosis (Figure) determined by the late gadolinium enhancement of cardiac magnetic imaging.



Cardiac magnetic resonance images.

Conclusion: Mutation carriers with founder MYBPC3 V762D can develop unfavorable phenotypes of HCM when combined with other sarcomere gene mutations.

P6165 | BEDSIDE
Immunosuppressive therapy limits myocardial damage and contractile dysfunction in eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

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Background: Cardiac involvement remains the major mortality predictor in eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss). The recognition of efficacy of immunosuppression to limit cardiac involvement may extend indications for immunosuppressive therapy in EGPA.
Objective: To assess the impact of addition of non-steroid immunosuppression to glucocorticoid therapy on cardiac disease in EGPA.
Methods: 51 patients (36 females, 15 males, mean age 44.3±14.4 years) with EGPA in clinical remission were retrospectively studied and scheduled for cardiac magnetic resonance (CMR) at follow-up. CMR images were assessed off-line for the presence of left ventricular ejection fraction (LVEF) <50% and myocardial damage depicted by late gadolinium enhancement (LGE).
Results: At diagnosis 15 patients presented with heart failure and 13 had LVEF<50%. At 39.2±38.7 months of follow-up, 25 patients demonstrated heart failure, 22 had LVEF<50%, and 29 LVLGE in CMR. Comparing subjects in whom non-steroid immunosuppressants were (n=18) and were not (n=33) initiated at diagnosis, the latter more frequently had new onset or progression of heart failure (1[6%] versus 12[36%], p=.02). The baseline and follow-up LVEF was either 58.3±14.1% and 56.8±14.2% (p=.30) or 54.8±12.3% and 49.9±17.7% (p=.02), when non-steroid immunosuppression was or was not introduced at diagnosis, respectively. Both the lack of introduction of non-steroid immunosuppression at diagnosis and non-steroid immunosuppression discontinuity index defined as ratio between treatment period without non-steroid immunosuppression and disease duration provided incremental predictive value over clinical data for the presence of LVLGE (odds ratio (OR)=23.55, 95% confidence interval (CI): 2.69-206.45, p=.004; OR=1.03 per 1%, 95%CI: 1.01-1.06, p=.01) and LVEF<50% (OR=16.11, 95%CI: 1.82-143.05, p=.01; OR=1.03 per 1%, 95%CI: 1.00-1.06, p=.03) at follow-up, respectively (p<.05 for increase in chi-square and area under curve). After adjustment for age, relapse rate, maximal blood eosinophilia, the extent of myocardial damage at follow-up expressed as LVLGE volume was associated with duration of non-steroid immunosuppression and non-steroid immunosuppression discontinuity index.
Conclusions: Non-steroid immunosuppressive therapy limits the extent of myocardial damage and dysfunction and may prevent development of heart failure in EGPA.

P6166 | BEDSIDE
Postoperative course and long-term prognosis of two chambered right ventricle

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Background: Two chambered right ventricle (TCRV), which is divided into two chambers by abnormal muscle bundle, is a rare disease. Most patients with TCRV were diagnosed in childhood or adolescence. The stenosis of TCRV is progressive, and early surgical intervention is recommended for patients whose symptom and/or pressure overload of RV inflow is progressive. However, there are few data about the postoperative course of TCRV and the surgical indication for asymptomatic patients is difficult.
Methods: We retrospectively investigated 38 consecutive patients who were diagnosed as TCRV and underwent surgical intervention between 1981 and 2009. Clinical background, pre and postoperative data of cardiac catheter, transthoracic echocardiography (TTE) and postoperative outcomes were evaluated. Moreover, we picked up 26 patients who were followed-up by TTE for more than two years and investigated postoperative recurrence by evaluating peak velocity of tricuspid regurgitation flow (TRVp) in pre-, postoperative and long-term followed-up TTE.
Results: The median age of surgical intervention was 5 years old (2-10.75 years old), and there were 4 patients with surgical intervention in adulthood. There were no perioperative death and complications. Among 38 patients, 37 patients complicated ventricle septal defect (type 1 in 4 patients, type 2 in 33 patients). In preoperative cardiac catheter, systolic pressure of RV inflow and peak pressure gradient between RV inflow and RV outflow were 82.1±32.1mmHg and 48.3±33.6mmHg, respectively. TRVp of pre and postoperative TTE were 4.2±0.8m/s and 2.4±0.6m/s. Mean follow-up period of 26 patients with long-term follow-up was 10.8±7.5years, and TRVp of long-term followed-up TTE was 2.3±0.5m/s. There were no death and no recurrence of TCRV (defined as TRVp≥3.0m/s) during postoperative long-term follow-up.
Conclusion: Surgical outcome and long-term prognosis of TCRV were good. There was no recurrence during long-term follow-up. Therefore, we should take into consideration early surgical intervention even for asymptomatic patients with TCRV.

P6167 | BEDSIDE
Conflicting gender-related differences during long-term followup of patients with Idiopathic Dilated Cardiomyopathy

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Background: Gender differences may affect disease presentation, clinical pathways, diagnostic yield and prognosis of patients with cardiovascular disease; few information about gender differences in idiopathic dilated cardiomyopathy (IDCM) are available.
We evaluated possible clinical, laboratory and prognostic divergences in women and men with IDCM.
Methods and results: From 1988 to 2012, 803 consecutive patients with IDCM recorded in the Heart Muscle Disease Registry of Trieste (Italy) were evaluated; 576 (72%) were male and 227 (28%) were female.
At first evaluation women were significantly older (48 vs. 45 years old, p=0.008); 62 (28%) of women and 134 (23%) of men presented with NYHA functional class III-IV (p=0.226).
Women showed more frequently a left bundle branch block at ECG (38% vs. 28%, p=0.01), smaller left ventricular end-diastolic indexed volume at echocardiography (85 vs. 93 ml/m^2, p<0.002) and more frequently moderate to severe mitral regurgitation at Doppler (43% vs. 33%, p=0.015). No difference among medical treatment and device implantation rate was found.
Interestingly, during a median 108 months follow-up period women showed less frequently a clinical and echocardiographic improvement, but a significantly lower ten-years total mortality/heart transplantation rate and cardiovascular mortality (20% vs. 32% (p=0.001), and 9% vs. 15% (p=0.024).
Conclusions: In our population of patients with IDCM, women present with a more advanced phase of the disease and a lower clinical-instrumental improvement on optimal medical therapy than men, notwithstanding that women have a better long-term prognosis.

P6168 | BEDSIDE
Evidence for altered cortisol stress responses in patients with takotsubo cardiomyopathy?

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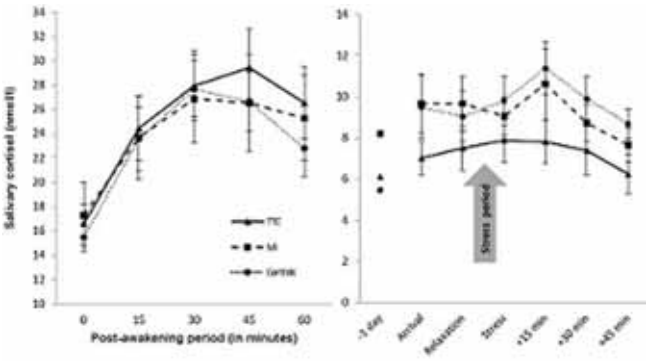
Purpose: In patients with takotsubo cardiomyopathy (TTC), a catecholamine increase can be observed after the stressful trigger event and psychiatric disorders, vulnerable personality traits and chronic stress were suggested as predisposing factors. Altered cortisol awakening and stress responses (CAR, CSR) are sensitive markers for the basal activity and responsiveness of the hypothalamus–pituitary–adrenal axis (HPAA) in psychopathological conditions. Now, these markers were investigated in TTC patients for the first time.
Methods: 19 female TTC patients were compared to 20 women with histories of myocardial infarction (MI) and to 20 healthy controls, matched by age and index event date. Repeated salivary sampling indicated cortisol release; questionnaires assessed personality, life events, chronic stress and psychiatric symptoms. Blood-sampling was not performed, because venipuncture itself can lead to HPAA activation.
Results: The groups did not differ in their basal HPAA activity, psychiatric or personality profiles. TTC patients revealed a significantly blunted cortisol stress response in contrast to controls [covariate: pre-stress cortisol; F(1,36)=4.35, p=0.044, r=0.33], despite increased heart rates and nervousness. The contrast TTC versus MI revealed no main effect on CSR [same covariate; F(1,36)=1.34, p=0.255, r=0.20]. Stressful life events occurred significantly more often in TTC patients.



Salivary cortisol.

Conclusions: In this small sample, a trend for a blunted CSR with medium effect sizes can be observed in TTC patients. In neuroendocrine research, reduced CSR due to chronic stress and the inhibitory influence of cortisol on catecholamine release are familiar. If blunted CSR can be confirmed in larger studies with adequate power levels, it may stimulate new avenues for the research in TTC.

CARDIOMYOPATHIES III

P6170 | BEDSIDE
Early and late onset of familial amyloid polyneuropathy: two distinct clinical phenotypes in terms of arrhythmias

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Background: Cardiovascular manifestations in familial amyloid polyneuropathy (FAP) TTR-V30M are the result of amyloid deposits in the heart causing infiltrative cardiomyopathy (arrhythmias and conduction disturbances) and autonomic neuropathy (blood pressure and heart rate control disturbances). Indeed, arrhythmias are very common in these patients, but their characterization is not fully studied.
Purpose: To assess the arrhythmic profile according to age of onset of symptoms (early vs. late) and its duration.
Methods: Prospective observational study of consecutive V30M-TTR mutation carriers. All patients were evaluated annually, including Holter monitoring. Multivariate Cox logistic regression analysis (stepwise forward conditional) adjusted for age was used to examine whether the risk of arrhythmias was independently associated with the age of clinical presentation and the duration of symptoms.
Results: We studied 223 patients (54.3% female, 44±14 years) that were followed for a median of 55 months. Of those, 162 were symptomatic: 102 had an early onset of symptoms (<50 years) and 60 had a late onset (≥50 years). From a total of 777 Holter recordings, 553 were performed in symptomatic patients. Tachyarrhythmias were detected in 55 exams and bradyarrhythmias in 211 exams. The overall risk of arrhythmic events was higher in patients with late onset disease (OR: 1.535, 95% CI 1.007-2.338, P=0.04) and in those with longer duration of symptoms (OR: 1.108, 95% CI 1.063 to 1.154, P<0.001). Regarding the risk of bradyarrhythmias the only significant difference was observed as a function of symptoms duration (OR: 1.105, 95% CI 1.062-1.15, P<0.001). The overall risk of tachyarrhythmias was significantly higher in patients with late onset of the disease (OR: 2.33, 95% CI 1.307-4.152, P=0.004) in which an increased risk of supra-ventricular tachyarrhythmia was noted (OR: 2.474; 95% CI 1.318–4.643, P=0.005), but not in the risk of ventricular tachycardia.
Conclusion: In FAP, early and late onset of the disease are two distinct phenotypes in terms of arrhythmias. Both forms have an increased risk of bradyarrhythmias, increasing their propensity as a function of symptoms duration. Regarding the risk of tachyarrhythmias there are clear differences, patients with late onset are at increased risk of supraventricular taquiarrythmias, particularly atrial fibrillation.

P6171 | BEDSIDE
Different biomarkers in the diagnosis of the inflammatory cardiomyopathy

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Aim: To evaluate the role of different biomarkers in the verification of the inflammatory cardiomyopathy (ICMP).
Methods: 35 patients mean age 40,8±11,3 (21 male, 14 female), I-III Class NYHA, mean LVEF 33,8±6,36%, with symptomatic heart failure for median 2,0 [1,0;3,0] years and suspected inflammatory cardiomyopathy underwent endomyocardial biopsy (EMB). EMB specimens were investigated with histological and molecular-genetic methods with PCR detection of cardiotropic viruses. Diagnosis was based on World Health Organization criteria. Leucocytes and macrophages criteria amount was ≥14. Sera were taken for testing different biomarkers.
Results: The total number of EMB patients was 35 (100%). ICMP was diagnosed in 15 cases (42, 8%) [9 cases (25, 7%) were virus-positive and 6 cases (17,1%) were virus-negative]. DCMP without signs of active inflammation was revealed in n=20 (57, 1%). [12 cases (34, 2%) were virus positive and 8 cases (22, 8%) were virus negative]. Mean NYHA FC was 2, 06±0, 77 in ICMP pts group and 2, 17±0, 7 in DCMP pts group (p=0,6). According to EMB results, in the myocardium of patients with ICMP the median of lymphocytes, expressing CD3+, CD4+ and CD8+ were 17,4 [9,0;23,0], 13,5[10,0;20,0] and 10,0 [6,0;11,7] relatively, that was significantly higher compared with group of DCMP without active inflammation: relatively 3,4[1,3;4,6] (p<0,0001) for CD3+, 1,8[0,0;3,2] (p<0,0001) for CD4+ and 3,1 [1,5;4,2](p<0,0001) for CD8+. Between the groups of ICMP and DCMP significant differences were revealed in the levels of the following biomarkers: hsCRP 3,6[1,0;6,7] vs 0,63 [0,8;2,0] (p=0,02); Anti-dsDNA (U/ml) 3,7[2,8;7,1] vs1,4[0,39;2,8] (p=0,008); C3 component of complement (g/l) 1,3[1,15;1,6] vs 1,18[1,0;1,3] (p=0,04); C4 component of complement 0,28 [0,21;0,35] vs 0,23 [0,18;0,28] (p=0,04); MMP9 (ng/ml) 657 [404;1668] vs 440 [317;637] (p=0,03); TGFβ pg/ml 12543 [3620;52676] vs 7030 [0,0;9956] (p=0,02) relatively. The level

of hsTNFα in pts with ICMP correlates with the severity of myocardial hypertrophy r=0,8 (p=0,01), severity of cardiosclerosis r=0,7 (p=0,02), ESV r=0,7 (p=0,009), EDV r=0,6 (p=0,04), EF r=-0,6 (p=0,06), NT-pro BNP =0,7 (p=0,007), ECP r=0,9 (p=0,005). SVCAM in pts with ICMP correlates with the severity of myocardial hypertrophy r=0,6 (p=0,03).
Conclusions: Compared with DCMP without signs of active inflammation the patients with ICMP have activation of inflammatory response, higher levels of TGFβ and metalloproteinases activity. In pts with ICMP hsTNFα secreting involves in myocardial fibrosis and hypertrophy.

P6172 | BEDSIDE
Intramyocardial fibrosis and muscle mass in hypertrophic cardiomyopathy: may cardiac CT and osteopontin contribute to diagnosis?

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Introduction: Ventricular fibrillation in Hypertrophic Cardiomyopathy (HCM) is partially due to intramyocardial fibrosis (IF). For IF assessment usually provided by cardiovascular magnetic resonance with late gadolinium enhancement (LGE-CMR) late enhanced computed tomography (leMDCT) and different serum-markers have been introduced. Convincing correlations have never been proven. By validating with LGE-CMR we tested leMDCT and a new fibrosis serum-marker, osteopontin, a secreted glycoprotein (OPN) in consecutive HCM patients with regard to IF and left-ventricular muscle mass (LV-MM).
Methods: We included 30 patients consecutively. For IF-assessment all individuals were conducted to LGE-CMR (1.5T, 32-channel coil,) and leMDCT (64-slice). In LGE-CMR data acquisition (Phase Sensitivity Inversion Recovery sequence) was performed 12 minutes after injection of Gadolinium Diethylenetriamines penta-acetic acid (0.15 mmoL/kgBW). LeMDCT scans were carried out 7 minutes after injection of 150mL iodiated dye (Iopromid, Iodine 350 mg/mL). Besides healthy controls all patients were taken blood samples for assessment of OPN levels (Human Osteopontin Assay; IBL). Finally, OPN was correlated with LGE-CMR-, leMDCT- and standard 2D echo-data.
Results: Mean age of patients and healthy controls was 62.4±14.7 vs. 56.6±7.2 years. LeMDCT detected IF in 19/30 patients (63.3%) validated by LGE-CMR. Tissue density of IF was 142±51HU vs. 89.9±19.3HU in remote myocardium; $p<0.001$. LV-MM and IF-mass was assessed by leMDCT with 151.3±46.8gMM and 8.4±5.2gIF vs. by LGE-CMR with 169.4±62gMM and 10.2±6.3gIF. Controls and HCM-patients presented an OPN level of 396.7±96.8ng/mL vs. 664±284.7ng/mL (p=0.0001). Controls vs. HCM-patients showed a significant difference in mean value of 267.3ng/mL (2sided T-Test; $p<0.0001$, 95%CI 165.8;368.8). IF quantified by leMDCT and LGE-CMR correlated with OPN: r=0.21 (p=0.37) and r=0.23 (p=0.33). Correlation of OPN with left-ventricular (LV) muscle mass (MM) assessed by LGE-CMR and leMDCT in HCM patients was r=0.52 (p=0.01) and r=0.56 (p=0.02). In contrast, OPN correlated weakly with calculated LV-MM (r=0.29, p=0.04) and E/A (Spearman-Rho=-0.25, p=0.08). There was no significant difference with regard to distribution of OPN in patients with HNCM, HOCM and apical HCM (p=0.43).
Conclusion: In consecutive HCM patients validated leMDCT reliably quantifies intramyocardial fibrosis. In contrast, Osteopontin and the extent of intramyocardial fibrosis and LV muscle mass showed an unexpectedly weak correlation. The diagnostic value of these new approaches should be further investigated in larger HCM cohorts.

P6173 | BEDSIDE
Female gender's disease - apical ballooning syndrome and ST-elevation myocardial infarction: long-term outcomes, mortality and survival

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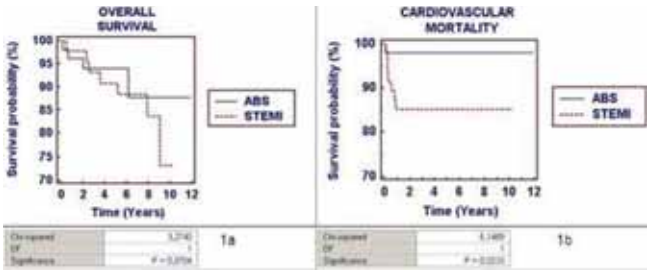
Purpose: To assess long-term outcomes and survival in women with Apical Ballooning Syndrome (ABS) and to compare those with STEMI patients (pts).
Methods: We reviewed 7446 pts admitted from 2001 until 2013 with diagnosis of acute coronary syndrome (ACS), of those 1905 were STEMI. From 2003 until 2007 data regarding mortality of 538 female STEMI pts were collected. From 2001-2013 all pts with on-admission typical ABS were selected (n. 69). We enrolled in the study 54/69 (78.3%) ABS with at least 1 year of follow-up. Survival were assessed and compared to a matching STEMI control group, comparable to our ABS population for age, sex, clinical characteristics and with at least 1 year of follow-up, consisted of 54/538 (10%).
Results: Mean age was 72.3±10.8 and 72.3±11.7 years and mean follow- up was of 56.10±36.69 and 71.45±38.94 months in ABS and STEMI respectively. 3.7% presented in-hospital MACE in ABS group and 13.0% in STEMI group. 30 days mortality was the same (1.85%) in both groups. ABS group survival was at: 1 year 94.4%, 5 years 92.5%, 10 years 90.7%. During 10 years of follow-up there were 5 deaths, (1 cardiovascular death). STEMI group survival was: 1 year 85.2%, 5 years 79.6%, 10 was 74.7%. During 10 years of follow-up there were 14 deaths, (7 cardiovascular deaths). No statistical differences in long term survival between STEMI and ABS group were found (p=0.07), (Figure 1a). Long term cardiovascular mortality was lower in ABS compared with STEMI pts (p=0.02), (Figure 1b).



Conclusions: Prevalence of ABS was 0,9% in pts admitted for ACS. ABS and STEMI pts have no significant difference in long-term survival. ABS pts presented a decrease risk of cardiovascular death when compared to STEMI group pointing out a different pathophysiologic mechanism.

P6174 | BEDSIDE
The response of the QTC interval to standing as a new diagnostic tool for long QT syndrome

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Background: The QT interval duration depends on the heart rate (HR) and is related with the autonomic nervous system regulation. Patients with Long QT Syndrome (LQTS) due to mutation of the potassium channels have an abnormal response to abrupt changes in HR and to the sympathetic stimulation that occurs with the brisk standing.
Objective: The purpose of our study was to describe the QT interval changes provoked by standing in a group of patients with congenital LQTS, and compare the changes with a group of unaffected relatives.
Methods: We performed an ECG in the supine position and another immediately after getting up in 26 patients with LQTS and 26 unaffected relatives. We measured the corrected QT interval (QTc) (Bazett's Formula) in supine position and immediately after standing in DII and V5 to assess whether there were differences in the QTc in both leads. We evaluated the increase in the QTc interval (ΔQTc = QTc in standing-QTc in supine).
Results: LQTS group consisted of 26 patients with genetic confirmation for LQTS (42±17 years, 50% males). Among LQTS patients, 6 (23%) had LQTS1, 17 (65%) had LQTS2, and 3 (12%) had LQTS7.In the control group the mean age was 40±15 years, and 44% were males. QTc values in supine and in standing positions are shown in Table 1. LQTS patients had a higher QTc interval after brisk standing than in supine position ($p<0.0001$ for both leads). In contrast, controls showed no significant increase in the QTc interval on standing. We also observed significant differences when compared the mean increase in the QTc interval between both groups ($p<0.0001$ for leads DII and V5). No significant differences in the increase of the QTc interval on standing were observed between LQT1 and LQT2 patients.

Table 1. QTc in supine and in standing positions

	QTc supine DII (ms)	QTc standing DII (ms)	ΔQTc DII (ms)	QTc supine V5 (ms)	QTc standing V5 (ms)	ΔQTc V5 (ms)
LQT gene + (n=26)	464±22	537±43	72±38	463±23	531±37	69±34
Controls (n=26)	411±20	419±16	8±15	410±20	418±17	9±14

Conclusions: Our population of patients with congenital LQTS had an abnormal QTc interval adaptation with the standing, showing a significant increase of this measure. These changes in the QTc interval were observed in both DII and V5 leads. Since our controls did not show this behavior, the performance of this test could be a useful tool in the diagnosis of individuals with baseline QTc interval at the upper limit of normal.

P6175 | BEDSIDE
QRS fragmentation or epsilon potentials in Fontaine leads in arrhythmogenic right ventricular cardiomyopathy

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Fontaine leads with highly amplified precordial leads and modified limb leads are often used to diagnose arrhythmogenic right ventricular cardiomyopathy according to a publication of Marcus and Fontaine published in 1984. In standard ECG leads epsilon waves could be found in about 23% of cases according to recent

literature. If these special leads are used epsilon waves are documented in much more cases. QRS fragmentation in standard ECG leads could be found in 85% of cases in arrhythmogenic right ventricular cardiomyopathy.
The question is whether these special leads can be used not only to increase the rate of epsilon waves but also the rate of QRS fragmentation. QRS fragmentation is defined as a notching of the Q wave, of the R wave or the S wave and includes epsilon waves, terminal activation delay and S wave upstroke.
Method: In a cohort of 128 patients (76 males, mean age of 46.3±13.1 years) Fontaine leads were used to diagnose arrhythmogenic right ventricular cardiomyopathy. Epsilon waves and QRS fragmentation were analyzed in highly amplified precordial leads and in modified limb leads.
Results: Epsilon waves could be found in Fontaine leads in n=99/128 (77%) of cases. QRS fragmentation could be demonstrated in n=127/128 (99%) of cases as additional notching of the Q wave and R wave. QRS fragmentation includes typical epsilon wave defined as notching of the S wave and beyond in the transition to the T wave.
Conclusions: If Fontaine leads are used in this cohort of patients with typical arrhythmogenic right ventricular cardiomyopathy the finding of epsilon waves increased dramatically by Fontaine leads but QRS fragmentation increased to a rate of 99% superior to epsilon wave discrimination. If QRS fragmentation in Fontaine leads are used the diagnosis of arrhythmogenic right ventricular cardiomyopathy can be made in almost all patients by highly amplified and modified ECG.

P6176 | BEDSIDE
Clinical significance of recurrence of extracardiac Ga-67 uptake in cardiac sarcoidosis during steroid therapy

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Background: Although the steroid administration has been established to improve prognosis in cardiac sarcoidosis (CA), there have been few reports of clinical indicators identifying inflammatory activity related to the titration of steroid. Clinical significance of recurrence of extracardiac Ga-67 uptake in CA, once disappeared by the introduction of steroid therapy, is not fully investigated.
Methods: We investigated 28 consecutive CA patients receiving steroid therapy in 2002-2012. Prednisolone was started at the dose of 30 mg/day for 1 month, and then tapered off by 5 mg every 4 weeks. Finally, the maintenance dose was 5 mg/day. The clinical examinations including Ga-67 scintigram were performed before the introduction of steroid, after the initial phase of prednisolone with 30 mg, and then repeated it once a year.
Results: Although intra- and/or extra-cardiac Ga-67 uptake disappeared in all cases after the steroid therapy, extra-cardiac Ga-67 uptake, mainly in the mediastinum, recurred in 13 patients in the process of tapered steroid. During the follow-up of 3.9±2.8 years, 7 cardiac events were observed including 2 sudden deaths, 2 ventricular tachycardia, 1 hospitalization with exacerbated heart failure, 1 newly diagnosed complete atrioventricular block and 1 chest pain without ischemic heart disease. When divided into 2 groups based on Ga-67 re-uptake (R+ or R-), there were no significant difference of the echocardiographic parameters between the 2 groups. Cardiac events were significantly occurred in R+ than R- (46% vs. 7% $P<0.05$), and left ventricular ejection fraction deteriorated more in R+ than R- (-(8±8) vs. +(4±7)%, $P<0.01$).
Conclusion: The recurrence of extra-cardiac Ga-67 uptake during the steroid therapy indicates poor prognosis, presumably through inadequate suppression of myocardial inflammation.

P6177 | BEDSIDE
Blood pressure alterations during heart failure treatment in patients with non-ischemic dilated cardiomyopathy

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Background: Most of cardioprotective agents to improve the prognosis of heart failure (HF) with reduced ejection fraction have no little effect on decreased systemic blood pressure (BP). Actually, the initiation and titration with optimal treatment were unfortunately limited in patients with low BP. We previously reported that systolic BP<113mmHg before the titration of HF medications was at high risk for cardiac events in patients with non-ischemic dilated cardiomyopathy (NIDCM). However, little is known about the BP alterations during cardioprotective treatment in HF patients with low BP.
Purpose: This study aimed to clarify the systolic BP alterations during the titration period of HF treatment and to investigate the prognostic value of BP alterations in low BP patients with asymptomatic or mildly symptomatic NIDCM.
Methods: We enrolled 65 NIDCM patients (22% female) with systolic BP<113Hg classified in NYHA functional class I or II. All patients underwent laboratory examination, echocardiography, and cardiac catheterization before the titration. We defined the BP before the titration of HF medications as pre-BP, the BP after the titration as post-BP, and the increase of BP (post-BP minus pre-BP) as ΔBP. The mean follow up period was 3.5 years.
Results: The mean age, left ventricular ejection fraction, BNP levels were 48.4 years, 29.8%, 335pg/mL, respectively. ACEi/ARBs, ß-blockers, and mineralocorticoid receptor antagonists were used in 80%, 94% and 62% of the patients before the titration and increased to 92%, 95% and 72% after the titration, respectively. The post-BP (102±14 mmHg) tends to be higher than the pre-BP (99±10 mmHg) (p=0.11) and BP levels in 37 (57%) patients were elevated after the titration. Univariate cox proportional hazard analysis revealed that post-BP and ΔBP had inverse correlation with the risk of cardiac events ($p<0.01$ and p=0.03, respectively). In multivariate analysis, post-BP was an independent determinant of cardiac events (p=0.04).
Conclusions: BP levels were elevated after the optimal treatment of HF in about 50% of NIDCM patients with low BP. Additionally, higher post-BP was associated with a lower risk of cardiac events. Those results implicate that we should not hesitate to use cardioprotective medications for NIDCM patients, even if their systolic BP is low.

P6178 | BENCH
Identification of novel markers in various cardiac pathologies for risk stratification and targeted therapy

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Purpose: Heart diseases are the leading causes of death worldwide. Dilated cardiomyopathy (DCM), myocarditis and ischemic cardiomyopathy (ICM) can be caused by various factors. The immune system is believed to play a central role after disease onset and during disease progression. Autoantibodies directed against various peptide-antigens present in cardiac tissue are found in these cardiac diseases.
Methods: Peptide Array analysis (PEPperMAP) with sera obtained from 10 DCM, 10 myocarditis, and ICM patients vs. 10 healthy, age-matched controls was performed against 26,364 different 15-mer peptides derived from 166 proteins associated with cardiovascular diseases.
A/JOla mice (n=8) were immunized on days 0, 7, 14 with peptide sequences (150μg) derived from identified proteins. On day 28, mice were sacrificed, histopathological evaluation of the heart and antibodies were determined within the serum.
Results: In the myocarditis group various antigens were observed such as the giant sarcomeric signaling protein obscurin, the cytoplasmic protein dystrophin and laminin which is present in the basal lamina, as well as regulatory enzymes such as myosin light chain kinase and sodium/potassium transporting ATPase. The most promising candidate antigens in the DCM group were the structural proteins obscurin, dystrophin and laminin. In fact, over 30% of the top 50 antigenic peptides represent obscurin. In addition, we also identified 4 strongly reacting antigenic oligopeptides derived from RNA-binding protein 20. Sera from ICM patients reacted strongly to peptides derived from laminin, sodium/potassium transporting ATPase located in the plasma membrane of the cell and the voltage-gated potassium channel KCNQ1 required for repolarization of the cardiac action potential. Furthermore, we could identify the heat shock protein HSP27, the AMP/ATP-binding subunit of the AMP-activated protein kinase, and actin.
Mice were only immunized with peptides found in the myocarditis and DCM groups. We identified inflammation and structural changes in mice immunized with RNA-binding protein 20 and myosin-binding protein C (fast-type).
Conclusion: In this study, novel target antigens for autoantibody binding in different cardiac diseases have been identified. Some antigens occur in more than one disease. The pathogenity of some of this autoantibody binding has been tested in animal models identifying novel target proteins. The results of this study can help to establish testing methods for risk stratification in patients and to design more efficient and more specific treatment methods.

P6179 | BEDSIDE
Dilated cardiomyopathy as a syndrome: results of differential diagnosis and specific treatment

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Purpose: To develop complex (clinical and morphological) approach to differentiall diagnosis and specific treatment of dilated cardiomyopathy (DCM).
Methods: In 130 patients with DCM syndrome (41 females, 46.9±12.5 years, the average left ventricle diastolic diameter 6.6±0.9 cm, EF 29.2±10.7%, systolic pulmonary pressure 44.8±16.5 mm Hg) were performed blood cardiotropic viruses (PCR) and anti-heart antibodies investigation, ECG, Holter monitoring, Echo-CG, cardiac CT, MRI, coronary angiography, and also morphological study of myocardium in 42 patients with PCR diagnostics. In control group (35 patients with noninflammatory heart disease, who underwent open-heart surgery, and 16 healthy volunteers) were serological and morphological markers of myocarditis investigated.
Results: The anti-heart antibodies titers was significantly higher in DCM compared with control group, and also frequency of viremia (26.9% vs 13.7%, $p<0.001$) and morphological signs of myocarditis (88.1% vs 25.0%, $p<0.001$), whereas was not differences in the incidence of detection of the viral genome in the myocardium (66.7% vs 77.1%). By comparing of morphological study and

noninvasive tests, the algorithm nosological diagnosis was developed. Isolated myocarditis diagnosed in 63% patients, its combination with genetic disorders in 17%, and genetic cardiomyopathy in 9%; in 11% patients a primary (idiopathic) cardiomyopathy was diagnosed. The anti-heart antibodies level had the most strong correlation with biopsy data.
In patients with inflammatory specific therapy was administered: methylprednisolon (32 [20; 40] mg/day), hydroxychloroquine 200 mg/day, azatioprine 108,3±34,2 mg/day, gancyclovir or acyclovir, IV immunoglobulin. Antiviral therapy was effective in 79.3% cases. Significant decrease ($p<0.05$) of left ventricle diastolic diameter (6.7±0.9 to 6.4±1.1), diastolic (202.7±85.0 to 177.9±96.4) and systolic volume (143.6±74.2 to 114.1±71.8), systolic pulmonary artery pressure (47.0±16.3 to 34.4±12.4), increase of EF (30.7±10.9 to 39.5±11.3) were found only in patients who received immunosuppressive therapy, both in virus-negative and virus-positive patients. With a mean follow-up 12.0 [5; 22] months mortality was 20.8%.
Conclusions: An complex clinical and morphological approach made it possible to verify nosologic nature of DCM syndrome and appoint an effective antiviral and immunosuppressive therapy. Immunosuppressive therapy is reasonable like virus-negative and-positive virus in patients with a high degree of immune activity as possible after the suppression of viral infection.

P6180 | BEDSIDE
Clinical significance of cardiac events and left ventricular systolic function improvement in newly-diagnosed dilated cardiomyopathy patients with prolonged QRS duration

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Purpose: Prolonged QRS duration is a risk factor for poor prognosis in patients with non-ischemic dilated cardiomyopathy (DCM). Cardiac resynchronization therapy is widely used for patients with heart failure (HF) patients with impaired left ventricular ejection fraction (LVEF) ≤35% and prolonged QRS duration. It has been unclear, however, the association between prognosis and LVEF improvement in newly-diagnosed DCM (ND-DCM) patients treated only optimal pharmacotherapy (OPT) with prolonged QRS.
Methods and results: One hundred and fifty three consecutive ND-DCM patients with LVEF ≤35% at baseline under OPT in 1996-2011 were enrolled. The patients were divided into 2 groups based on the QRS duration: ≥120 msec (Group C; n=40) or <120 msec (Group N; n=113). Group C was further divided into 2 groups based on LVEF >35% (Group C1; n=24) or LVEF ≤35% (Group C2; n=16) during 6 months after completing OPT. None of Group C died during 6 months. During the observational period for 1778±1220 days, there were 4 deaths as the primary endpoint and 11 composite of cardiovascular events including readmission for worsening HF and major ventricular arrhythmias as the secondary endpoint. Kaplan-Meier curves indicated significantly fewer primary (P=0.016) or secondary endpoints (P=0.029) in Group C1 than in Group C2. On the other hand, there was no significant difference of both end points between the group N and group C1 (Fig. 1A, B).

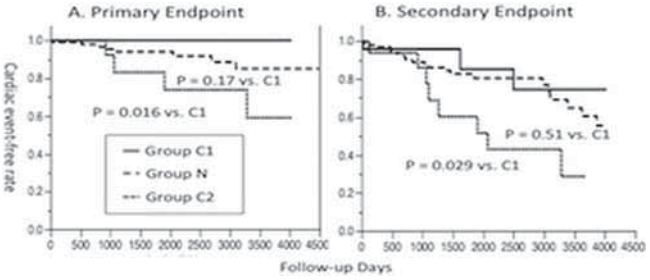

Figure 1

Conclusion: There were some ND-DCM patients with QRS ≥120 msec at baseline whose LVEF improved after completing OPT. The clinical outcome of ND-DCM patients with QRS ≥120 msec with LVEF improvement during 6 months were equivalent to that of the ND-DCM patients with QRS <120 msec. Further studies will be necessary to identify patients with QRS≥120msec who can respond to OPT.

P6181 | BEDSIDE
Low left ventricular function and high troponin i level in acute phase predict delayed recovery in patients with takotsubo cardiomyopathy

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Background: Takotsubo cardiomyopathy (TC) is characterized by transient reversible systolic dysfunction of the apical and/or mid segments of the left ventricle (LV). However, there is little information about the details of its recovery process. The present study evaluated recovery process and the contributing factors in TC patients.
Methods: A total of 16 consecutive patients with TC underwent serial cardiovascular magnetic resonance imaging (CMR) (acute phase 3.25±1.88 day and follow-up 57.6±42.3 day) to assess global LV ejection fraction (LVEF) and regional LV wall motion. Furthermore, myocardial edema defined as high intensity area in T2-weighted CMR was evaluated.
Results: Between acute phase and follow-up, global LVEF improved from 48±13% to 68±9%. Regional wall motion abnormality remained in 4 patients (25.0%) in the follow-up CMR. Myocardial edema was observed in 13 patients (81%) in acute phase and follow-up CMR showed it in 9 patients (69.2%). Of 16 patients, 12 had no regional LV wall motion abnormality in the follow-up CMR and 4 had incomplete recovery. Lower global LVEF (34.5% vs 52.5%, $p<0.01$) and higher troponin I level (8.66 vs 2.61 ng/ml, p=0.04) in acute phase were observed in patients with incomplete recovery of regional LV wall motion.
Conclusions: Regional LV wall motion abnormality and myocardial edema do not disappear in all TC patients. Low global LVEF and high troponin I level in acute phase are predictors of delayed recovery in TC patients.

CARDIOMYOPATHIES IV

P6183 | BEDSIDE
Different response to adaptive servo-ventilation therapy according to the etiology of cardiomyopathy in patients with chronic heart failure

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Background: Beneficial effect of adaptive servo-ventilation (ASV) therapy in patients with chronic heart failure (CHF) has been reported. However, the difference in responsiveness to ASV therapy between the causes of cardiomyopathy is unexplored.
Methods: ASV therapy was successfully introduced in a total of 136 CHF patients between February 2009 and March 2013. Patients with LVEF >40%, valvular heart disease, or specific myocardial diseases were excluded; thereafter, 105 consecutive patients were enrolled in the study. They were divided clinically into dilated cardiomyopathy (DCM, n=70), dilated phase of hypertrophic cardiomyopathy (dHCM, n=16), and ischemic cardiomyopathy (ICM, n=19). Patients were followed up to a mean period of 300 days. Laboratory and echo data were obtained before and 6 months after ASV introduction. Baseline data including plasma BNP, hemoglobin, serum creatinine, serum sodium concentration, and medications were not different among groups.
Results: Six months of ASV therapy provided significant increase of LVEF in patients with DCM (6.1±1.1%, p=0.04) compared with dHCM (-0.1±3.0%) and ICM (0.4±2.6%). Kaplan-Meier analysis demonstrated that dHCM patients were associated with increased risk of death or heart failure readmission compared with DCM and ICM patients (p=0.02, Fig. 1).

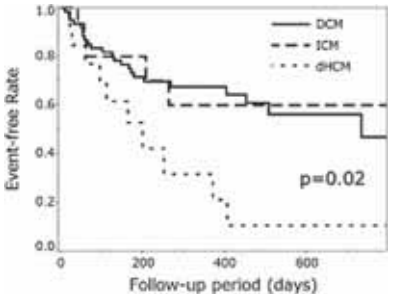

Figure 1. Survival analysis.

Conclusions: ASV therapy improved cardiac function in DCM patients, while dHCM patients showed poor clinical outcome even after ASV therapy.

P6184 | BEDSIDE
Dried blood spot screening of Fabry Disease among patients with left ventricular hypertrophy of unknown cause

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Purpose: Identifying subjects and genotypic profiles compatible with Fabry Dis-

ease (FD) by dried blood spot (DBS) screening, among left ventricular hypertrophy (LVH) patients ≥18 years, as candidates for genetic study of the α-galactosidase A gene (GLA) due to their gender and their low α-galactosidase A (α-Gal A)activity.
Methods: Screening study for FD among patients attending to cardiologist departments with unexplained left ventricular hypertrophy (≥14mm). DBS α-Gal A activity from patients was compared against controls matched by gender and medical center. Male patients with enzymatic activity <70% of controls and all female patients, underwent GLA gene sequencing characterization.
Results: A total of 369 patients were screened, 249 males (67.8%) which were younger than females (58±16 vs 65±15 years old; p<0.001). Overall, patients were overweighed on average (BMI = 28±8 kg/cm^2), the septal wall thickness was 19.4±4.7mm and the more frequent LVH geometry patterns were concentric and asymmetric (42% and 40%, respectively). Females showed a higher percentage of arterial hypertension (58.8% vs 45.4%; p=0.015), but no differences were shown in their creatinine levels 1.01±0.76 vs 1.12±0.71 mg/dl).
The GLA gene was sequenced for 67 males (26.9% among males) and all females, finding different variants in 18 males and 42 Females. Classical FD mutation c.376 A>G (p.S126G), previously reported, was found in 1 subject (0.3%); 4 unrelated subjects were found carriers of c.937 G>T (p.D313Y) variant, previously associated with enzyme pseudo-deficiency; other 55 subjects showed variants located in promoter and/or intronic regions. From these subjects, 15 patients showed a Complex Haplotype (CH) type I (-10 c>t, c.376-81_77 del5, c.640-16 A>G, c.1000-22 C>T); 17 patients showed a CH II (c.376-81_77 del5, c.640-16 A>G, c.1000-22 C>T); 15 patients showed a CH III (c.-12 g>a, c.548-125 C>G, c.639+68 A>G, c.1000-22 C>T) and one patient showed a combined CH II and III. In addition, we have identified 3 novel variants c.-34 c>t, c.192 C>T (p.I64=) and c.640-25 A>G whose significance in FD pathology remains unknown.
Conclusions: Only one subject (0.3%) showed a classical missense mutation in FD, however 48 subjects (13.3%) showed several complex haplotypes (CH) previously described in individuals with FD symptoms. Further studies are needed to link those CH that might participate in the presentations of FD.

P6185 | BEDSIDE
Increased levels of Carbohydrate-Antigen-125 at admission predicts hospital stay and incidence of adverse events in stress cardiomyopathy

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Background: Biomarker activation during stress cardiomyopathy is still not well known.
Carbohydrate-antigen (CA)-125, however, was studied as risk marker in subjects with chronic and acute heart failure. We therefore aimed to evaluate possible role of CA-125 in risk stratification and its possible correlations with other clinical characteristics in subject with stress cardiomyopathy.
Methods: Thirty-nine consecutive subjects with stress cardiomyopathy were enrolled in the study and followed for a mean 347±493 days. Circulating levels of CA-125, NT-proBNP, left ventricular ejection fraction (LVEF), presence of dyspnea and ST-elevation at electrocardiogram were evaluated at admission. The duration of hospital stay and the incidence of death, cardiovascular death, readmission and recurrence of stress cardiomyopathy during follow-up were also reported.
Results: Mean hospital stay was 8±3 days, 8% of subjects incurred adverse events during follow up. Circulating levels of CA-125 at admission were inversely related to LVEF (r -0.36, p<0.05) and directly related to hospital stay (r 0.37, p<0.05). Correlation with NT-proBNP levels was of borderline significance (r 0.34, p 0.059).
Circulating levels of CA-125 were higher in subjects with adverse events at follow-up (250±381 vs 19±30 U/mL). Higher levels of CA-125 were associated with higher rates of adverse events at follow up even after multivariable correction for age, gender, NT-pro-BNP levels, presence of dyspnea and ST-elevation (relative risk 1.005, 95% confidence interval 1-1.011, p<0.05).
At ROC curve analysis, CA-125 levels >16.8 U/mL anticipated the incidence of adverse events with 100% sensitivity, 78% specificity, and 100% negative predictive power (area under curve 0.889).
Conclusions: 125 admission levels are associated with longer hospital stay, lower LVEF, and higher risk of adverse events during follow up.

P6186 | BEDSIDE
Myocardial insult in idiopathic inflammatory myopathies: continuum of skeletal muscles and myocardium

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Purpose: Idiopathic, inflammatory myopathies (IIMs) are a group of rare muscle disorders comprised of polymyositis (PM), dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM) and the sporadic form of inclusion-body myositis. Although cardiovascular disease is among the leading causes of death in patients with IIMs, the prevalence of cardiovascular involvement in these patients is unknown. The aim of the present study was to assess the myocardial performance in patients with IIMs.
Methods: We studied fifteen patients with DM and PM, without clinically overt cardiovascular disease. All patients underwent a full cardiac evaluation including electrocardiogram (ECG), transthoracic echocardiogram (TTE), cardiac magnetic resonance (CMR) and 24h ECG recording. Patients with impaired left ventricular function (ejection fraction, EF≤50%) were subject to coronary angiography for exclusion of coronary artery disease. Electrophysiologic study was performed in patients with evidence of non-sustained ventricular tachycardia at the 24h ECG recording. Laboratory exams included measurement of CPK, transaminases (ALT, AST), high-sensitivity C-reactive protein (hsCRP), troponin I and brain natriuretic peptide (BNP).
Results: The mean age of patients was 53 years and five patients were males (33%). Most of the patients (n=12) were under treatment with corticosteroids. Levels of CPK (1052.7±2381 IU/L), ALT (51.4±69.9 IU/L), AST (57.7±68.4 IU/L) and hsCRP (6.7±6.2 mg/L) were increased, whereas troponin I (0.01±0.03 ng/ml) and BNP (57.0±42.1 pg/ml) concentrations were within normal limits. TTE showed reduced EF≤50% in 3 out of 15 patients (33%) with absence of coronary artery disease in the subsequent coronary angiography. CMR was positive for myocardial fibrosis in 4 patients (25% of the study participants). The presence of myocardial fibrosis was related to age (r=-0.63, p=0.03) and EF (r=-0.71, p=0.02). Two patients (13%) had signs of non-sustained ventricular tachycardia at the 24h ECG recording and the following electrophysiologic study, performed in one of the two patients, demonstrated inducible ventricular tachycardia, hemodynamically compromised.
Conclusions: A high prevalence of myocardial damage was identified in patients with IIMs, mainly due to inflammation-mediated fibrosis. Given the high cardiovascular mortality in these patients, cardiovascular risk stratification through comprehensive step by step evaluation is essential and should be implemented in all patients with IIMs.

P6187 | BEDSIDE
T-cell-receptor Vbeta dominance indicates antigen specificity of infiltrates in myocarditis and dilated or inflammatory cardiomyopathy

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Introduction: Antiviral and autoimmune pathomechanisms contribute to the pathogenic link between myocarditis (MC) and DCM. Increased T-cell infiltrates, a key diagnostic criterion for inflammatory cardiomyopathy (DCMi), are detectable in a substantial fraction of patients presenting with dilated cardiomyopathy (DCM). T-cell responses targeting specific antigens can lead to a restriction of the T-cell-receptor Vbeta (TCR Vb) repertoire. The former TCR Vb nomenclature has been updated by the TRBV classification (ImMunoGeneTics).
Diverse TCR Vbeta and TRBV dominances have been associated with several immune diseases.
Aims: Systematic evaluation of publications on TCR Vbeta / TRBV dominance in experimental and human MC / DCM / DCMi.
Results: Dominances of TCR Vb10, Vb8 and Vb13 were identified in Coxsackievirus B (CVB) induced murine MC. Dominant TCR Vb4 infiltrates were elucidated in experimental autoimmune MC in rats. CDR3 spectratyping revealed dominance of TCR Vb3, Vb7, Vb13.1 Vb1 and Vb5B in human DCM. This finding was associated to CVB infection (detected by immunohistology). In Chagas cardiomyopathy, abundance of TCR Vb 4, Vb 5, Vb 11, Vb 13, Vb 17 and Vb 20 have been analyzed. Significant associations between the immunohistological proof of DCMi and the expression of the constant TRB region (TRBC) and of CD3d have been established using a preamplified real-time RT-PCR for TRBC and TRBV gene expression. DCMi, however, was not characterized by a particular TRBV dominance per se. In contrast, differential TRBV dominances were associated with the PCR proof of viral genomes in human DCMi: TRBV11 and TRBV14 with Parvovirus B19 (B19V); TRBV4, TRBV10 and TRBV28 with human Herpes virus type 6 (HHV6); and TRBV14 with Enterovirus. In a patient presenting with acute myocarditis and B19V viremia, TRBV11 dominance was detected in the peripheral blood leukocytes.
Conclusions: Restrictions of TCR Vbeta repertoire of the T-cell infiltrates are present both in experimental CVB induced myocarditis and in autoimmune AMC in rodents. CDR3 spectratyping confirmed diverse TCR Vb dominances in CVB and in Chagas induced human DCM. Increased TRBC expression is associated with the immunohistological criteria of DCMi. Furthermore, the detectability of diverse viral genomes by PCR is associated with differential TRBV dominances in human DCM. These data confirm the hypothesis that distinct antigens may induce and maintain the intramyocardial T-cell infiltrates both in experimental and in human MC and DCMi. These insights might be relevant for immunomodulatory treatment strategies targeting the T-cell response in MC and DCMi.

P6188 | BENCH
Surgical correction of HOCM in patients with severe hypertrophy and myocardial fibrosis

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Background: In patients with hypertrophic cardiomyopathy myocardial fibrosis is an independent predictor of adverse outcome. A new technique of HOCM surgical correction in patients with extreme hypertrophy and septal myocardial fibrosis has been proposed.
Methods: The excision of the asymmetrical hypertrophied area of the interventricular septum (IVS) causing obstruction was performed from the conal part of the right ventricle corresponding to the zone obstruction of the left ventricle (LV). This excision was carried out on the right side of the IVS and not trough the whole IVS thickness. The areas of septal myocardial fibrosis were removed corresponding to the zone of delayed enhancement (DE) imaging. Myocardial fibrosis was detected by cardiovascular magnetic resonance with DE imaging. Nine HOCM patients with extreme hypertrophy (NYHA Class 3,1), myocardial fibrosis and episodes of ventricular tachycardia (VT) underwent this procedure. Five patients had biventricular obstruction. The follow-up period was 39±9 months.
Results: Seven patients were free of symptoms (NYHA class 1) and two patients had only mild limitations. The mean echocardiographic gradient in LV decreased from 89,9±12,6 to 9,1±2,2 mmHg, the mean value of gradient in right ventricular outflow tract was reduced from 43,4±5,2 to 4,3±1,3 mmHg. Echocardiographically determined septal thickness was reduced from 34,7±3,1 to 15,6±2,1mm. Sinus rhythm without block of His bundle right branch was noted in all patients after surgery. VT was not registered. None of the patients needed implantation of cardioverter-defibrillator.
Conclusion: This novel technique of HOCM surgical correction provides the precise removal of the areas of septal fibroisis and effective elimination of biventricular obstruction in patients with extreme hypertrophy who can not be treated with the current surgical techniques. The approach avoids mechanical damage to the heart conduction system.

P6189 | BEDSIDE
Prevalence and treatment of chromosomally integrated human herpesvirus 6 in patients with symptomatic heart failure

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Objective: Investigation of prevalence, germline transmission and reactivation of HHV-6 in patients with persisting unexplained heart failure. Human herpesvirus 6 (HHV-6) A and B are two betaherpesviruses that are associated with many conditions including roseola, drug induced hypersensitivity syndrome, liver failure and myocarditis. HHV-6 is integrated in the germ line (ciHHV-6) in about 0.8% of the human population. Until now, the prevalence, species distribution and treatment responses of ciHHV-6 are unknown for cardiac patients.
Methods: We determined the prevalence of HHV-6 and ciHHV-6 genotypes in 1656 endomyocardial biopsies of patients with persisting unexplained heart failure. Infection of cardiac tissue was identified by nPCR, electron microscopy and immunohistochemistry. Virus load and mRNA levels were followed in ciHHV-6 patients treated with ganciclovir.
Results: HHV-6 was detected in 273 of 1656 cardiac tissues (16.5%, HHV-6B: 98.2%, HHV-6A: 1.8%) by PCR. Nineteen of the 1656 patients (1.1%) presented with persisting high HHV-6 copy numbers indicative of ciHHV-6. Sequencing confirmed ciHHV-6A in 7 patients (36.8%) which was considerably higher than detected in non-ciHHV-6 patients or described for normal populations. Inheritance was demonstrated in 3 selected families confirming ciHHV-6 chromosomal integration by PCR and by FISH. HHV-6 reactivation and chromosomal integration were confirmed in PBMCs and heart tissue. Virus particles were identified in degenerating myocytes and interstitial cells. Antiviral treatment abolished viral mRNA and ameliorated cardiac symptoms.
Conclusion: Virus replication in cardiac tissue of ciHHV6 heart failure patients suggests that ciHHV-6 reactivation causes persistence of unexplained heart failure symptoms. We demonstrated that antiviral treatment, effective in decreasing viral transcripts and clinical complaints of cardiomyopathies, is a new therapeutic option for ciHHV6 associated diseases.

P6190 | BEDSIDE
Added diagnostic value of multiplex ligation-dependent probe amplification of plakophilin-2 in arrhythmogenic cardiomyopathy

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Background: Arrhythmogenic Cardiomyopathy (ACM) is an autosomal dominant disease characterized by progressive fibro-fatty infiltration and high frequency of ventricular arrhythmias that can lead to sudden death. It is mainly caused by mutation in genes encoding desmosomal components, involved in only ~50% of patients.
Aim: The present study aimed to determine the frequency and prevalence of desmosomal genes mutations in a small cohort and to investigate whether copy number variations (CNVs) detection may increase the diagnostic yield of genetic screening in ACM.
Methods: 60 ACM consecutive patients underwent direct sequencing on a ABI-PRISM 3730 for 5 ACM-associated genes. Multiplex Ligation-dependent Probe Amplification by SALSA MLPA P168 ARVC-PKP2 kit and quantitative Real-Time PCR (qPCR) on a Light Cycler 480 were performed on genotype-negative probands in search of CNVs in Plakophilin-2 (PKP2).
Results: This comprehensive screening revealed pathogenic point mutations in 36 index patients (60%) distributed as follows: 5 mutations in Desmoglein-2 (8%), 14 in Desmoplakin (23%), 7 in PKP2 (12%), 2 in Desmocollin-2 (3%), 2 in Plakoglobin (3%), 6 cases (10%) with multiple mutations, and 1 heterozygous large PKP2 exon deletion in 1 otherwise genotype-negative patient (2%). This new deletion was detected by MLPA technique and then confirmed by relative qPCR.
Conclusions: Screening analysis of ACM-related genes in 60 ACM index cases displayed approximately 60% of mutation carriers by conventional sequencing and another 2% by MLPA analysis, highlighting the potential of this CNVs analysis in increasing the diagnostic yield up to 10%.

P6191 | BEDSIDE
Heart rate turbulence analysis as a markers of risk myocardium electrical instability and sudden cardiac death in children with hypertrophic cardiomyopathy

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Purpose: To evaluate the heart rate turbulence parameters in children with hypertrophic cardiomyopathy (HCM).
Methods: We examined 53 children with HCM (40 boys and 13 girls, mean age 13 [7;17]). Cardiac examination included standard electrocardiogram (ESG), Doppler echocardiography, 24-hour ESG monitoring. HRT parameters: turbullence onset (TO)- and turbullence slope (TS) were analyzed, if the number of ventricular premature complexes (VPC) was >5 and 2400/recording. Patients (pts) with atrial fibrillation, pacemaker rhythm or absence of VPCs were excluded. HRT was considered abnormal when TO ≥%0 or TS ≤2,5 ms/RR interval.
Results: According to modern criteria HRT analysis was possible to make in 24 of 53 (45%) patients (pts) with HCM. The average values of TO were -2.47±0,94% (ranged from -8.45 to 8.15). Pathological values of TO >0% (ranged from 0.84 to 8.5) were detected in 5 from 24 patients (20.8%). In all patients with abnormal values of TO were observed one or more major risk factors of sudden cardiac death: unexplained syncope (3pts), severe left ventricular hypertrophy (more than 30 mm) (4pts), non-sustain ventricular tachycardia (4pts), family history of sudden cardiac death (1pts). We obtained the relationship between pathological values of TO and non-sustain ventricular tachycardia (p=0,0076), and syncope (p<0,05). The average value of TS was 16,87±2,4 ms/RR (ranged from 3.8 to 42.3). TS value <2.5 was not revealed in all patients. The value TS <6 was observed in 3 patients.
Conclusions: Pathological values of THR (TO) revealed in 5 from 24 children with HCM. Abnormal parameters of TO were associated with non-sustain ventricular tachycardia and syncope. Electrical instability of myocardium according to TPT analysis in the combination with other risk factors of sudden cardiac death may be a new indication for implantation of a cardioverter - defibrillator in children with HCM.

PERICARDIAL AND MYOCARDIAL DISEASE

P6193 | BEDSIDE
Various clinical features and echocardiographic profile of cardiac myxomas

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Background: Cardiac myxoma is a benign neoplasm that represents the most common primary tumour of the heart. Although the left atrium is the most commonly involved site of origin in 75% of cases, it can arise from any of the cardiac chambers.
Aim: To see clinical and echocardiohgraphic profile of 72 cardiac myoxomas.
Methods: 72 cardiac myxomas patients who admitted in National Institute of Cardiovascular Diseases from August 2003 to December, 2012 were studied clinically and by echocardiogram.
Results: There were 18 males and 54 females, ages ranged from 17 to 76 years. The commonest symptom was dyspnoea (85%), followed by constitutional symptoms (42.4%), embolization (21.5%), palpitation (22.9%), syncope (13.2%), pedal oedema (18.6%) and chest discomfort (67.4%). The mean duration of symptoms was 09.7 months. Only in 7.9% cases was the diagnosis of myxomas made clinically. 73.7% cases were initially diagnosed as having: mitral valve disease, tricuspid valve disease (09%), ischemic heart disease (3.4%), cardiomyopathy (1.7%), and the remaining 4.3% were detected during family screening and follow-up. The sites of myxomas were left atrium 67; right atrium, 4; and, biatrium1. All

myxomas except 5 were attached to the interatrial septum. The site, size, shape, attachment, mobility, prolapse into ventricle, and surface characteristic of myxomas were accurately assessed by 2D-echocardiography.When the morphological characteristic of myxomas were studied and correlated with clinical features large left atrial myxoma size was closely related with constitutional symptoms, congestive heart failure, with syncope and auscultatory findings suggestive of mitral valve disease, whereas smaller myxoma size and irregular surface were associated with embolization.
Conclusion: Majority of myxomas mimic many cardiovascular diseases and were detected in symptomatic patients, so a high index of clinical suspicion is important for its early and correct diagnosis. The size and appearance of the myxomas correlated with the presenting symptoms.

P6194 | BEDSIDE
Clandestine subaortic stenosis as a cause of left ventricular outflow tract obstruction in patients with hypertrophic obstructive cardiomyopathy

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Introduction: Hypertrophic cardiomyopathy (HCM) has a prevalence of 1:500 in the general population and 70% of patients (pts) have intraventricular obstruction (HOCM). Membranous subaortic stenosis represents 6,5% of congenital heart disease, can lead to massive left ventricular hypertrophy, and might cause similar symptoms as HOCM (dyspnea, angina, syncope).
Methods: Between 1/2012 and 9/2013 165 consecutive patients (mean age 58±15 years, 45% female) with prediagnosed HCM were admitted to our department for therapy decision. Most (53%) were in NYHA III/IV, 23% had positive HCM family history, 54% had additional hypertension and 41% coronary artery disease. Atrial fibrillation was present in 18%, while 9% had an ICD. Mean septal thickness was 21±5 mm, mean left atrial diameter was 47±7 mm, mean left ventricular ouflow tract (LVOT) gradient was 50±39 mmHg at rest and 87±52 mmHg with Valsalva maneouvre.
Results: 24 (14%) pts had non-obstructive HCM (mean septal thickness 20±6 mm, left atrial diameter 48±11 mm) while 138 (84%) pts had HOCM (mean septal thickness 21±4 mm, left atrial diameter 47±6 mm). LVOT gradient was 57±38 mmHg at rest and 100±46 mmHg with Valsalva. In 3 (2%) pts, a subaortic membrane, suspected with transthoracic and ascertained with transesophageal echocardiography, was the cause of LVOT obstruction. In those pts (mean septal thickness 25±12 mm, left atrium diameter 39±1 mm) LVOT gradient was 63±22 mmHg at rest and 83±18 mmHg with Valsalva, while 1 pt had an ICD for primary prevention of sudden death. In this last pt subaortic membrane coincided with HOCM (histological proof of extensive disarray in the myectomy specimen).
Conclusions: Subaortic membrane is an important differential diagnosis of hypertrophic obstructive cardiomyopathy. Transthoracic and transesophageal echocardiography (including colour, CW and PW Doppler with focus on LVOT) are the basic noninvasive tools for subaortic membrane detection. Resection of the subaortic membrane with myectomy should include histology of resected myocardium, as diagnosis of coexistent HCM may have implications on risk stratification for sudden cardiac death.

P6195 | BEDSIDE
Left ventricular function in treatment-naive early rheumatoid arthritis

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Background: The role of inflammation in the pathogenesis of cardiovascular disease in rheumatoid arthritis (RA) remains unclear.
Objective: We investigated how disease activity, anti-cyclic citrullinated peptide antibodies (anti-CCP) status and coronary calcium score in treatment-naive early RA, impacts left ventricular (LV) systolic function.
Methods: Fifty-tree patients with mean age 58.3±1.3 years and steroid- and disease-modifying antirheumatic drug (DMARD)-naive early RA were included. Disease activity was scored by the use of the Danish national DANBIO registry (number of swollen joints (NSJ (28)), number of tender joints (NTJ (28)), C-reactive protein (CRP) and Health Assessment Questionnaire (HAQ)). Pain, fatigue, patient and physician global assessment and a composite disease activity score (DAS28-CRP) were assessed by visual analog scales (VAS) 0–100. IgM rheumafactor (IgM-RF) and anti-CCP titers were evaluated by standardized techniques. Coronary calcium score was estimated by computed tomography (CT) by calculating the Agaston score. One experienced senior rheumatologist and one experienced cardiologist performed all the clinical assessments as well as all the transthoracic echocardiography (TTE) and coronary CT analysis.
Results: We found LV systolic function by conventional ejection fraction to be 54.1±9.2% and to be non-significant correlated to disease activity (CRP: r=0.07, p=0.64; baseline NSJ: r=-0.13, p=0.33; NTJ: r=-0.08, p=0.58; HAQ: r=0.23, p=0.1; pain VAS: r=-0.05, p=0.74; fatigue VAS: r=0.03, p=0,83; physician global assessment: r=-0.09, p=0.54 and DAS28: r=-0.03, p=0.84).
Using global longitudinal systolic strain (GLS), a more sensitive measurement of the LV function we found a significant correlation: HAQ (r=0.29; p=0.037), patient global assessment by VAS (r=0.35; p=0,.011), patient fatigue assessment by VAS (r=0.3; p=0.03) and DAS28-CRP (r=0.28; p=0.043); all corrected for relevant confounders. Furthermore, anti-CCP was highly significantly correlated with GLS (r=-0.44; p=0.001) in univariate analysis. In multivariate analysis, it still remained significantly correlated (p=0.018), after correction for relevant confounders.
Using strain analysis of LV function, we found a significant difference in GLS in patients with high values of anti-CCP (titers ≥340) compared to patients with anti-CCP (titers <340); (-19.9±2.1% vs. -16.4±2.8%; p=0.0001). For patients with high IgM-RF, results were non-significant.
Conclusions: We observed a significant correlation between increased disease activity and cardiac function in treatment-naive early RA without ischemic heart disease.

P6196 | BEDSIDE
Relationship between left ventricular mass index and cardiac toxicity from anticancer agents

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Purpose: Administration of cardiotoxic anticancer agents results in a significant increase in left ventricular mass (LVM), and the rate of change (%) in LVM (ΔLVM) correlates with the total amount of anticancer agent (cyclophosphamide, epirubicin, and fluorouracil [5-FU]; CEF) per LVM (ΣCEF/LVM). This study investigated the difference between lower and higher LVM index (LVMI) patients.
Methods: We selected 276 consecutive breast cancer patients (all females; mean age, 52±9.7 years) who completed adjuvant chemotherapy with three drugs (CEF) over an 84-month period. These patients were categorized into the following two groups: LVMI <120 (group A; mean age, 43±5.4 years; n=243) and LVMI≧120 (group B; mean age, 58±7.9 years; n=33). Echocardiography was performed both before and after several cycles of CEF, and the following parameter were then calculated: left atrial diameter (LAD); LV diameter in diastole/systole (LVDd/s); LV end-diastolic volume (LVEDV); LV end-systolic volume (LVESV); interventricular septal thickness (IVST); posterior wall thickness (PWT); LV ejection fraction (LVEF); ratio of early to late ventricular filling velocity (E/A); mitral annulus velocity (e'); E/e'; Tei index (TI); relative wall thickness (RWT); LVM; LVMI; diameter of inferior vena cava (IVC); and systolic blood pressure (BPs). We also analyzed the relationship between ΣCEF/LVM and ΔLVM. Data were then compared between the two groups.
Results: Symptomatic heart failure was not observed in any case. Overall, no significant changes were observed in the indices of cardiac function, including LAD, LVEF, Tei-Index, A/E ratio, E/e' and IVC. On the other hand, after treatment with the anticancer drugs, significant increases were observed in LVDd/s, LVEDV, LVESV, IVST, PWT, RWT, LVM ($P<0.00001$) and LVMI ($p<0.00001$). Concerning BPs, a significant decrease was observed after the treatment ($p<0.001$). Moreover, ΣCEF/LVM correlated well with ΔLVM (r=0.42, $P<0.00001$, y=0.78x-15). Similar findings were observed in group A. On the other hand, in group B, no significant changes were observed in IVST, PWT, e', e/E, LVM or LVMI; however, significant decreases were seen in both RWT and IVC. A stronger correlation was observed between ΣCEF/LVM and ΔLVM in group A when compared with group B.
Conclusion: A cardiotoxic anticancer regimen resulted in an increase in LVM, with a tendency towards concentric hypertrophy, and induced heart failure with preserved ejection fraction (HF-PEF). This tendency was more common in patients with lower LVMI than in those with higher LVMI.

P6197 | BEDSIDE
Brain natriuretic peptide predicts mortality in patients undergoing pericardiectomy for constrictive pericarditis

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Purpose: Brain natriuretic peptide (BNP) levels are usually low despite severe signs and symptoms of heart failure in constrictive pericarditis (CP). Many clinical and demographic data are well known as risk predictors of mortality after pericardiectomy for CP. Nevertheless, the role of BNP on this setting is not clear.The aim of this study was to assess the utility of plasma BNP as a mortality risk predictor in CP patients submitted to pericardiectomy.
Methods: We studied retrospectively 57 patients submitted to radical pericardiectomy for CP between January 2002 and November 2013 in a tertiary hospital. All patients had blood tests for brain natriuretic peptide at admission. Clinical and surgical data, blood tests, echocardiography and cardiac magnetic resonance imaging were collected from the patient's medical records. All patients were followed-up by medical records or phone contact. Receiver operating characteristic (ROC) analyses was performed to identify the best BNP value in discriminating mortality.
Results: Mean age was 40.8±18 years with predominance of men (77.6%). CP etiology was: idiopathic (70.7%), tuberculosis (17.2%),post cardiac surgery (5.2%), systemic inflammatory disease (5.2%) and mediastinal radiotherapy (1.7%). There were 6 deaths in the first ninety days after surgery, 5 due to cardiogenic shock and 1 due to septic shock. Based on ROC curve the BNP value of 320 pg/dL provided sensitivity of 83% and specificity of 90.2%for predicting death. The area under the curve was 0.89. On univariate analyses urgent surgery, hemoglobin, systolic pulmonary pressure >55 mmHg and BNP>320

pg/dL (OR: 46, IC 4.4-476.1; p<0.0001) correlated to death. On multivariate analyses, only BNP remained as independent predictor of death (OR: 48.7, IC 4.5-527.2; p<0.0001).
Conclusion: This is the first study to show that elevated plasma levels of brain natriuretic peptide independently correlate with death in patients undergoing pericardiectomy for constrictive pericarditis. These findings may aid in the risk stratification of patients considered for surgery in this life-threatening disease.

P6198 | BEDSIDE
Cardiac involvement of systemic lupus erythematosus echocardiographic findings of 75 cases

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Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by inflammation of multiple organs. The heart may be seriously involved.
Aim of study: To investigate the cardiac involvement in patients diagnosed with SLE assessed from an echocardiographic view.
Methods: We retrospectively reviewed the records of 75 patients with diagnosis of SLE based on the American College of Rheumatology criteria and who were referred to our echocardiography laboratory between 1993 and 2012. All echocardiographic exams were carried by transthoracic way.
Results: Patients were female in 92% of cases. Mean age was 27.8 years (16-70 years). Echocardiography showed 17 cases (22%) of minim or moderate pericardial effusion, tamponade in 2 cases. Valvular abnormalities were observed in 19 cases (25%), this included thickening of valves in all cases associated to 6 cases of significant mitral regurgitation and 2 cases of Libman sacks mitral valve endocarditis. However, aortic involvement was noted only in 3 cases resulting in thickening and mild regurgitation. Myocardium was involved in 5 cases (6%) including dilated left ventricular in 3 cases and hypertrophy in 2 cases. Systolic dysfunction was noted in 2 cases, isolated diastolic left ventricular dysfunction in 10 patients. (13%). High arterial pulmonary hypertension was reported in 8 cases (10%) with mean systolic pulmonary arterial pressure was 59 mmHg (38-120 mmHg).
Conclusion: Patients with SLE have an increased risk of cardiac involvment. In agreement with previous reports, our study shows that pericardial effusion is the most frequent cardiac complication of lupus. Valvular involvement is relatively frequent but the degree of valvular dysfunction is generally not important. Early diastolic left ventricular dysfunction threaten seriously these patients. Echocardiography should be used as a screening tool, including annual echocardio-graphic screening of asymptomatic individuals with SLE

P6199 | BEDSIDE
Echocardiographic features of cardiac angiosarcomas: Mayo Clinic experience

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Introduction: Cardiac angiosarcoma, though exceedingly rare, is the most common primary malignant cardiac tumor. The dismal prognosis and non-specific symptomatology underscores the need for an accurate and cost effective approach to the identification and characterization of these rare tumors.
Methods: We searched the our clinic tissue registry for all histologically confirmed cases of cardiac angiosarcoma from January 1976 to the December 2013. This search strategy identified 33 cases, including 17 patients (mean age 46; 6 male, 11 female) who had echocardiograms available for review. The remaining 16 cases were comprised of outside referrals specifically for Oncologic consultation. Echocardiograms were retrospectively reviewed by the authors.
Results: TTE correctly identified primary cardiac angiosarcoma in 9 of 12 patients (sensitivity=75%) when performed as the initial diagnostic test. TTE TEE and CT all failed to identify cardiac angiosarcoma in one patient presenting with tamponade. Pericardial tumor extension was common and a pericardial effusion was present in 15 of 17 patients (88%), however, pericardial fluid analysis was invariably negative for malignancy. Left ventricular function was preserved in 16 of 17 patients, with an average ejection fraction of 62% and right ventricular function was mildly reduced in 2 of 17 patients at initial presentation. Tricuspid inflow obstruction was present in 3 patients, with a mean diastolic gradient of 6.3 mm Hg (range 3-11 mmHg).
Conclusions: We report the largest single center review describing the echocardiographic features of primary cardiac angiosarcoma. The sensitivity of TTE as the first diagnostic imaging modality was 75% (9 of 12 cases) and compared favorably with CT (3 of 4, 75%). Pericardial effusion is a common finding; however, pericardial fluid cytology was negative in all 15 patients who underwent percardiocentesis. The absence of a stalk was a universal finding and may help distinguish angiosarcoma from benign, primarily pedunculated tumors including myxoma and papillary fibroelastoma.

P6200 | BEDSIDE
Emery dreifuss-6 with peculiar x linked cardiomyopathy

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Purpose: FHL1 mutations cause a rare X-linked Emery Dreifuss Muscular Dystrophy (EDMD) variant. We aim to describe a family with type6 EDMD and severe cardiac phenotype.
Methods: Complete anamnesis and physical exam, blood tests, chest and spine X-ray, ECG, echocardiogram, neurologic, pneumologic and clinical genetics evaluation were obtained.
Results: 14/28 (50%) subjects (3males/12females) were carriers of a FHL1 p.Cys255Ser mutation (c.135292105G>C) (penetrance: 100% males; 29% females). Moderate (16-18mm max wall thickness) non-obstructive asymmetric hypertrophy with severe diastolic dysfunction and early severe systolic dysfunction was identified in all males and 1 (8%) female. Males had persistent CPK elevation (average: 304 UI/L). Early atrial flutter-fibrillation was identified in 100% of males and remarkable prolongation of the QT interval in 1 male. 1 male died suddenly aged 45 yrs and 1 female died aged 45 yrs after long-course cardiac disease. 1 male (proband) had resuscitated cardiac arrest (VF) aged 32 yrs. Cardiac transplant was performed in 2 males aged 51 and 52yrs. Examination of the explanted heart diagnosed mixed cardiomyopathy with Arrythmogenic Dysplasia and Left Ventricle non Compaction.
Skeletal muscle disease was identified in all males and 2 female carriers. Females displayed mild spinal deformity and CPK elevation. One 12yr-old girl associated thigh myalgia with exercise. Joint contractures, muscular hypertrophy/weakness and axial rigidity were identified in all males (including 15yr old obligated male carrier with no cardiac involvement). Lumbar hyperlordosis and/or thoracic kiphoscoliosis were identified in all males and 2 females. Persistent long-course mild thrombopenia was identified in proband.
Conclusions: We present a family with a FHL1 mutation causing EDMD-6 and X linked severe cardiac phenotype characterized by moderate hypertrophy, restrictive physiology with progression to severe heart failure and transplant. Despite echocardiogram, pathology reveals fibrofatty replacement of the myocardium and non-compaction.

P6201 | BEDSIDE
Left ventricular hypertrabeculation/noncompaction and pregnancy

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Background: Left ventricular hypertrabeculation/noncompaction (LVHT) is characterized by extensive trabeculations and a two-layered structure of the left ventricular myocardium. Aim of the study was to summarize outcomes of pregnancies in a LVHT cohort.
Methods: All females in whom LVHT was diagnosed in one echocardiographic laboratory when they were younger than 45 years were contacted in July 2013. It was asked if pregnancy or delivery occurred after the diagnosis of LVHT had been established.
Results: From 1995-2013 LVHT was diagnosed in 207 patients. In 22 of the 63 female patients LVHT had been diagnosed when they were younger than 45 years. In July 2013, 4 of the 21 surviving females reported uneventful pregnancies and deliveries after LVHT had been diagnosed. Delivery was vaginal in 3, in the fourth, caesarean section was carried out because of breech presentation. These 4 females never suffered from heart failure and their systolic function was normal. Clinical and echocardiographic findings did not differ between the females who did and did not become pregnant.
Conclusions: LVHT per se is no contraindication for pregnancy. If LVHT is diagnosed in females of childbearing age, cardiac risk associated with pregnancy can be estimated by scores considering previous cardiac events or arrhythmia, NYHA class of heart failure, presence of left heart obstruction and left ventricular ejection fraction. Since the data about pregnancy and LVHT are still rare, patients should be encouraged for cardiological follow-up and their data, including neurological findings, should be collected in registries.

P6202 | BEDSIDE
Malignant pericardial effusion: natural history and clinical features in the current era

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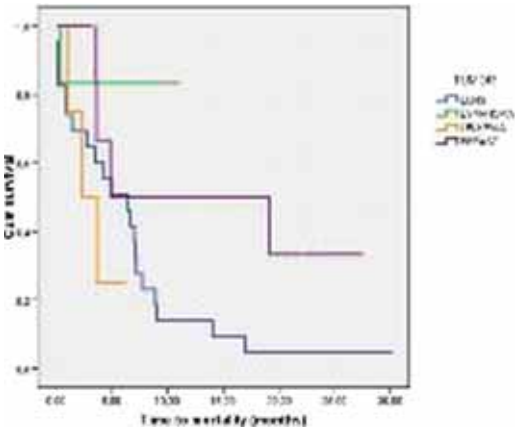
Introduction: Neoplastic disease is a rising etiology of pericardial effusion (PE). Its natural history and prognosis remain uncertain.

Objectives: To know the characteristics, natural history and prognostic implications of malignant pericardial effusions (MPE).
Methods: Patients with MPE were included from January 2010 to December 2013.
Results: 55 patients were analyzed (mean age 59 years, SD: 17, 51% male) with a mean follow up of 7 months (SD: 8). The PE was the neoplasia's first manifestation in 20%. Dyspnea was the most common symptom (33%). 51% required PE drainage, due to clinical (n=17) or echocardiographic (n=8) tamponade. 70% of the patients died, 3 of them due to cardiac tamponade and the rest as a consequence of disease progression. The mean time since diagnosis of MPE to death was 5 months (SD: 6). Only the type of tumor and the severity of PE were associated with higher mortality (p=0.05). 82% of patients received treatment for their underlying malignancy, which increased survival time (8 months vs 2 months, p=0.001).

Mortality and survival time

Type of cancer	Follow up (days) Mean/Median*	Mortality	Survival (days) Mean/Median*
Lung (n=22)	142 (2–927)*	20 (91%)	142 (SD: 119)
Breast (n=7)	148 (103–842)*	4 (57%)	129 (109–584)*
Leukemia (n=4)	103 (SD: 73)	3 (75%)	71 (SD: 41)
Lymphoma (n=7)	254 (SD: 167)	2 (29%)	264 (SD: 360)

(n = no. of patients. *Median if data do not meet criteria for normality.



Patient survival curves.

Conclusions: Mortality of MPE is determined by the primary cancer and the magnitude of the PE. Treatment of the underlying malignancy influences in survival time.

MYOCARDIAL AND PERICARDIAL DISEASE

P6204 | BEDSIDE
Pericarditis and myopericarditis/perimyocarditis: different prognosis?

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Introduction: Acute pericarditis (AP) and myopericarditis/perimyocarditis (MPPM) are inflammatory diseases of the heart whose natural history and prognosis are still poorly understood. The aim of the present study was to compare the prognosis of these two entities.
Methods: We retrospectively analyzed the clinical files of all patients admitted with AP and MPPM between January 2008 and December 2012. The diagnosis of AP was based on the presence of at least two of the following criteria: typical chest pain, pericardial rub, widespread ST-segment elevation or PR depression, and new or worsening pericardial effusion. MPPM was considered in the cases of suspected pericardial disease associated with elevated troponin levels, with or without reduced left ventricular systolic function or wall motion abnormalities.
Results: Fifty nine patients were included, 27 with AP and 32 with MPPM. The groups had equal sex distribution and the median age was significantly superior in the AP population (54 Vs 41 years; p=0.039). During hospitalization heart failure and higher levels of pro-BNP were more frequent in the MPPM patients, although without statistical significance. There were 3 cases of supraventricular tachycardia in the AP group and 1 in the MPPM, 1 case of sinus bradycardia and 1 atrioventricular blockage in both populations. The median peak troponin T level was 0.98 pg/mL (minimum 0.127; maximum 7.48) in the MPPM population. In this group, 7 patients (21.7%) presented left ventricular systolic dysfunction on echocardiogram which normalized/improved in a mean follow-up of 9 months (median initial ejection fraction 44%; final 58%). None of these cases had left ventricle dilatation. In a mean follow-up of 22 months heart failure diagnosis was made in 1 patient in each group. Recurrence was more common in the AP population (n=4; 14,8% Vs n=1) although without statistical significance. One patient with MPPM died during hospitalization and one patient admitted with AP died 10 months after the hospitalization due to a non-cardiovascular cause.
Conclusions: In our study MPPM and AP groups had similar outcomes. Elevated levels of troponin and reduced left ventricular function weren't, in our patients, linked to a worse prognosis.

P6205 | SPOTLIGHT
Tuberculous pericarditis is associated with impaired left and right ventricular myocardial mechanics measured by 2D-Speckle tracking echocardiography

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Background: Tuberculosis (TB) is a serious problem in developing countries, which account for 95% of worldwide TB cases, and 99% of worldwide TB mortality. TB has not been on the list as one of the leading causes of left ventricular systolic dysfunction and two-dimensional speckle tracking echocardiography (2D-STE) imaging has not been used routinely to assess ventricular function in tuberculosis pericarditis. The main of this study was to use 2D-STE to evaluate both the left (LV) and right (RV) ventricular systolic function.
Methods: A total of eighty two patients with the diagnosis of tuberculosis pericarditis, and suitable standard two-dimensional echocardiographic images were included in the study. Mean age of 33years (56% males). Their retrospective images were analyzed offline using velocity-vector imaging technology. Student t-test, Pearson correlation coefficient (r) was used to describe the relationship between echocardiographic and strain parameters. Multivariate linear regression analysis was used to investigate the association global circumferential and radial strain with the patients' symptoms and mortality.
Results: TB pericarditis is associated with significantly impaired LV strain both longitudinal and circumferential ($p<0.001$). Right ventricular free wall strain was also reduced in 40% of the patents. There was a strong negative correlation between LV systolic strain with LV ejection fraction (LVEF) based on the 2D-echocardiograph. There was a strong LV-RV and LV-Septal wall strain interaction ($p<0.001$). There was also no strong correlation between patients' symptoms and the severity of LV strain impairment. The presents of concomitant human defiffiency viral (HIV) infection pre-antiretroviral exposure was also associated with more severe LV strain impairment. After adjusting for patients' age, gender and body mass index LV systolic strain was predictive of poor LV function acutely.
Conclusion: Tuberculosis pericarditis is associated with both LV and RV strain impairment and the concomitant HIV status does play a role with the severity of LV dysfunction.

P6206 | BENCH
Myocardial performance index for detection of subclinical abnormalities in patients with sarcoidosis

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Aim: The aim of this study was to evaluate ventricular functions in patients with sarcoidosis without an obvious heart disease by using tissue Doppler-derived left and right ventricular myocardial performance index (MPI).
Methods: The study population included 45 patient with sarcoidosis (29 men, 16 women; mean age, 44±10 years, mean disease duration, 4.2±2.7 years) and 45 healthy control subjects (31 men, 14 women; mean age, 41±8 years). Cardiac functions were determined using echocardiography, consisting of standard two-dimensional and conventional Doppler and tissue Doppler imaging (TDI).
Results: The conventional echocardiographic parameters and tissue Doppler measurements were similar between the patients and controls. Left ventricular MPI (0.490±0.092 vs. 0.396±0.088, p=0.010) and right ventricular MPI (0.482±0.132 vs. 0.368±0.090, p=0.006) were significantly higher in patients with sarcoidosis than the control subjects. There was a correlation between the disease duration and right and left ventricular MPI (r=0.418, p=0.005; r=0.366, p=0.013, respectively) (Fig. 1). There was also a correlation between the systolic pulmonary arterial pressure and right ventricular MPI but not left ventricular MPI (r=0.370, p=0.012; r=0.248, p=0.109, respectively).

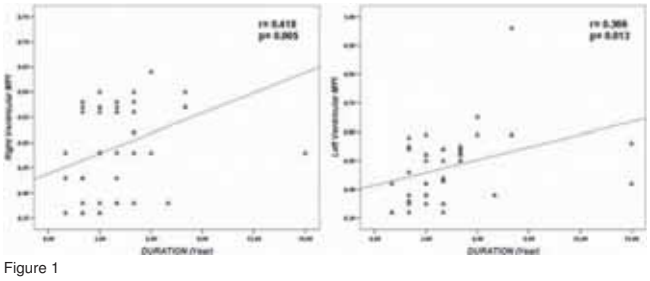

Figure 1

Conclusions: We have demonstrated that tissue Doppler-derived myocardial left and right ventricular MPI were impaired in sarcoidosis patients, although systolic and diastolic function parameters were comparable in the patients and controls. We also showed a correlation between the systolic pulmonary arterial pressure and right ventricular MPI in patients with sarcoidosis.

P6207 | BEDSIDE
The relation of echocardiographic epicardial adipose tissue thickness and the coronary artery disease

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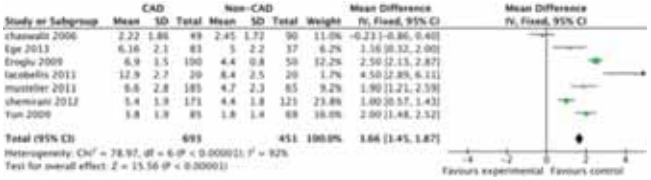
Background: Several studies suggested that epicardial adipose tissue (EAT) may be associated with coronary artery disease (CAD). EAT thickness can be measured by echocardiography. A meta-analysis was performed to investigate the relationship between echocardiographic EAT thickness and the CAD.
Methods: A systemic search of Pubmed, Cochrane and Medline from January 2003 to May 2013 was conducted for reports on echocardiographic EAT thickness in patients with and without the CAD using specific search terms such as "epicardial adipose tissue", "epicardial fat", "coronary artery disease". Data were extracted from applicable articles and mean differences or risk ratio, including 95% confidence intervals (CI), were calculated using RevMan 5.2 software.
Results: Seven studies were identified. The pooled population consisted of 1,144 subjects, of whom 693 had the CAD. Comparing with the non-CAD group, EAT thickness was significantly higher in patients in the CAD group (mean difference 1.66 mm, 95% CI 1.45 to 1.87, P<0.0001).



Conclusion: Echocariographic EAT thickness is significantly higher in patients with the CAD, and seems to be effective marker in the prediction of CAD.

P6208 | BEDSIDE
Impact of modified immunosuppression and neurohumoral blockade on prevention of ventricular remodeling and improved clinical outcome in patients with cardiac sarcoidosis

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Background: We previously surveyed the prognosis of cardiac sarcoidosis (CS) diagnosed before 1997 and identified the severity of heart failure and ventricular remodeling as independent predictors of mortality. During the past few decades, we have introduced modified immunosuppression including a higher maintenance dose of prednisolone (PSL) and addition of methotrexate (MTX), and neurohumoral blockade for heart failure in the treatment of CS. We therefore hypothesized that the prognosis of CS improves due to such advances in the medical treatment.
Methods: To confirm our hypothesis, we analyzed 45 CS patients diagnosed between 1988 and 2007 and treated with corticosteroids. We classified two sequential referral patients diagnosed between 1988 and 1997 (n=19) and between 1998 and 2007 (n=26), and compared treatment and prognosis.
Results: Although the severity of heart failure and echocardiographic variables were similar between the two cohorts, survival in the 1988-1997 referral cohort was significantly worse (Log-rank=4.41, p<0.05). The 1998-2007 referral cohort showed significantly higher incidence of renin-angiotensin-aldosterone inhibitors (69% versus 42%, p<0.05), β-blocker use (46% versus 6%, p<0.01) and addition of MTX (27% versus 0%, p<0.05), and increased maintenance dose of PSL (7.6±2.0 versus 5.0±0.9 mg/day, p<0.01) compared to the 1988-1997 cohort. Multivariate analysis identified diagnosis between 1988 and 1997 (hazard ratio[HR]=19.8, p<0.01) and left ventricular ejection fraction (LVEF) (HR=0.83/1% increase, p<0.01) as independent predictors of mortality. Addition of MTX improved diabetes (HbA1c: 7.6±1.9 to 7.2±2.0%, p<0.05) and lipid profile (triglyceride levels: 226±124 to 167±118 mg/dL, p<0.05) associated with reduced maintenance dose of PSL (8.3±3.4 to 6.4±2.2 mg/day, p<0.05). In patients with 5-year survivor of the recent cohort, LVEF was significantly improved (42±15 to 53±15%, p<0.01) and LV diameter was unchanged (49±9 to 51±9mm, n.s.) during the follow-up periods.
Conclusion: Modified immunosuppression and neurohumoral blockade may prevent ventricular remodeling and improve clinical outcome in patients with CS.

P6209 | BEDSIDE
Detection of myocardial injury by three-dimensional speckle tracking echocardiography in chronic hepatitis C infection

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Purpose: Although recent reports highlighted extra-hepatic manifestations of hepatitis C virus (HCV) in a variety of organs, right ventricular involvement is the most frequent cardiac alteration whereas a clear-cut left ventricular (LV) involvement has been never reported. Accordingly, aim of the study was to evaluate LV geometry and function by standard 2D and 3D echocardiography in a series of patients with HCV.
Methods: Twenty-four consecutive asymptomatic patients with chronic HCV (mean age = 60.9±6.5 yrs) and 20 normal controls (NC), comparable for age and gender prevalence, were compared by standard echo-Doppler, 2D Speckle Tracking Echocardiography (STE) and 3D (both volumetric and STE) echocardiography. Global longitudinal strain (GLS) was calculated by 2D STE whereas LV volumes and ejection fraction (EF), sphericity index, LV mass and 3D STE derived GLS, global circumferential strain (GCS), global area strain (GAS) and global radial strain (GRS) were also measured. Diagnosis of chronic hepatitis was based on liver biopsy or hepatic fibroScan. Cardiac images were acquired before the beginning of any kind of specific hepatic therapy. Coronary artery and valvular heart disease, heart failure, cardiomyopathies, atrial fibrillation, alcohol abuse, other causes of liver disease were exclusion criteria.
Results: The 2 groups were comparable for body mass index, heart rate and blood pressure. By standard 2D echocardiography no difference of 2D-derived EF, relative wall thickness, LV mass, E velocity deceleration time and E/e' ratio was found between HCV and NC. Only transmitral E/A ratio was marginally lower in HCV (0.84±0.2) than in NC (1.01±0.3) (p=0.04). Also the intergroup difference of 2D derived GLS and of 3D volumetric analysis (LV volumes, EF, sphericity index, LV mass) did not achieve the statistical difference. 3D STE showed lower GCS (HCV= -15.3±2.2%, NC = -17.6±3.9%, p=0.02), GAS (-25.5±2.6% vs.-29.9±5.2%, p=0.03) and GRS (37.6±4.6% vs 44.9±12%, p=0.04) whereas HCV-related changes of GLS were not significant.
Conclusion: Our findings demonstrate that 3D STE is able to detect subclinical alteration of LV myocardial dysfunction which cannot be diagnosed by both standard echo and 2D STE-derived GLS. Alteration involves circumferential fibers of midwall (GCS) and the composite deformation component represented by GAS whereas the longitudinal fibers of the subendocardial layer of myocardium appears to be preserved.

P6210 | BENCH
The critical role of autophagy on cardiomyocyte death during longterm high-fat diet stimulation

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Autophagy is an important process in the pathogenesis of cardiovascular diseases, and high-fat diet (HFD)-induced obesity plays a causative role in the induction of cardiomyocyte autophagy. The aims of this study were to elucidate the role of autophagy on the HFD-induced apoptosis of cardiac cells.
Methods and results: C57B/6J male mice (5 wk old) fed with the HFD for 24 wks induced obesity, hyperglycemia, and dyslipidemia. Chronically feeding the HFD caused heart hypertrophy and increased the protein expression of LC3II, caspase 12, and PARP in the heart. The in vitro cell model was further conducted to explore the role of autophagy on the HFD-induced cardiomyocyte death. Palmitate treatment (400 μM) for 24 hrs induced apoptosis in H9C2 cells, with increased expression of the autophagy markers LC3II and p62. An increase in the accumulation of autophagic vacuoles was observed in H9C2 cells exposed to palmitate. Palmitate decreased the expression of unfolded protein response (UPR) marker CHOP and GRP94, while increased the expression of endoplasmic reticulum (ER) stress-induced apoptosis marker caspase 12. Blocking this autophagic response with 3-methyladenine resulted in a significant increase in cell death and apoptosis of palmitate-treated H9C2 cells, with a further decreased expression of CHOP and GRP94. To summarize, the response of autophagy plays a critical role in HFD-induced apoptosis. Autophagy is essential for cariomycoyte survival when exposure to the HFD; however, excessive autophagy damaged the cellular functions and caused the apoptosis of cardiac cells. In addition, there is a crosstalk between autophagy and ER stress when exposing to the HFD, and this underlying mechanism needs further study.

P6211 | BEDSIDE
Comprehensive echocardiographic and BNP monitoring of patients with chronic Chagas disease

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Purpose: The number of patients with Chagas disease residing in Europe has increased significantly. Early detection of myocardial involvement in these patients is crucial due to prognostic implications. Our aim was to evaluate changes in echocardiographic parameters, including diastolic function and 2D myocardial strain and BNP levels in the follow-up of patients with chronic Chagas disease.
Methods: 20 subjects (40±13 years, 67% women) from endemic areas of Chagas disease (8 in the undetermined form of Chagas disease, 8 with chagasic cardiomyopathy and 4 non-infected controls) were evaluated with echocardiography, including diastolic function assessment and myocardial speckle-tracking, and BNP quantification at baseline and 3.5 (range 2.6-4.6) years later. Echocardiographic analysis was performed, using EchoPac software, blinded to patients' group and clinical or serologic results.

Results: There was a significant association between changes in circumferential and longitudinal myocardial strain, diastolic function and BNP levels (Fig. 1).

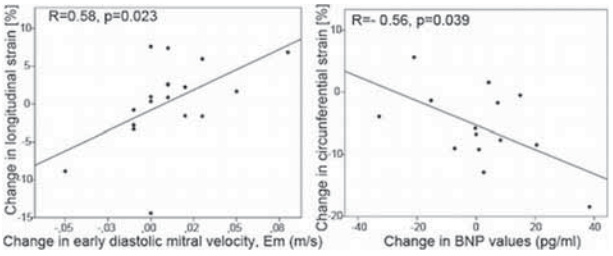

Figure 1. Association between strain, Em and BNP.

Conclusion: In the follow-up of patients with Chagas disease changes in myocardial strain correlates with changes in BNP and parameters of diastolic function. Those are complementary indices that may help to early detect myocardial involvement and to monitor mild left ventricular dysfunction in these patients.

P6212 | BEDSIDE
Cardiovascular changes in patients with non-severe Plasmodium vivax malaria

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Purpose: Cardiovascular system involvement in patients with Plasmodium vivax malaria has been poorly addressed. The aim of this study was to evaluate cardiac structures and function and serum markers of cardiovascular injury in patients with the non-severe form of Plasmodium vivax malaria.
Methods: We prospectively evaluated 26 patients with P. vivax malaria in an outpatient referral hospital from January 2012 to March 2013 and compared results with a control group of 25 gender- and age-matched healthy individuals. Patients underwent clinical evaluation, laboratory tests and transthoracic echocardiography at first evaluation after malaria diagnosis.
Results: Echocardiography showed higher left ventricular (LV) systolic diameter (28.8±2.82 vs 30.9±4.03 mm; p=0.037) and LV diastolic volume (82.4±12.3 vs 93.8±25.9 ml; p=0.05), and lower LV ejection fraction (Teicholz method: 73.2±6.59 vs 68.4±4.87; p=0.004) values in patients than controls. Right ventricle (RV) fractional area change (54.7±5.11 vs 50.5±6.71%; p=0.014) was lower, and RV myocardial performance index (0.21±0.71 vs 0.33±0.19; p=0.007), RV diastolic area (13.0±3.19 vs 15.3±2.96 cm^2; p=0.009) and systolic area (6.41±1.27 vs 7.45±1.46 cm^2; p=0.009), and pulmonary vascular resistance (1.13±0.25 vs 1.32±0.26 Woods unit; p=0.012) were higher in patients than controls. Patients presented higher serum levels of indirect bilirubin (0.24±0.15 vs 1.30±0.89 mg/dL; p<0.001), soluble vascular cell adhesion molecule–1 (sVCAM-1; 453±143 vs 1,983±880 ng/mL; p<0.001), N-terminal prohormone brain natriuretic peptide (0.59±0.86 vs 1.08±0.81 pg/mL; p=0.045), and troponin T (861±338 vs 1,037±264 pg/mL; p=0.045), and lower levels of nitric oxide (13.42±8.15 vs 8.98±3.97 μM; p=0.016) than controls.
Conclusion: Patients with non-severe Plasmodium vivax malaria present cardiac and endothelial functional alterations.

P6213 | BEDSIDE
Parasympathetic incompetence detected by heart rate variability analysis in deceleration phase during head-up tilt table test in chronic Chagas disease

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Introduction: In chronic Chagas disease (CCC), autonomic function is compromised in both sympathetic and parasympathetic limbs. Phase-rectification of RR interval series allows separation of acceleration (AC) and deceleration (DC) phases, which reflects sympathetic and parasympathetic influence on heart rate, respectively. The aim of this study was to assess autonomic function using heart rate variability (HRV) driven by phase-rectification in healthy and CCC subjects during head-up tilt table test (HUTT).
Methods: Healthy sedentary (HG, n=20) and CCC subjects (CG, n=20), age and gender matched, were studied. All underwent drug free 60min at 60° HUTT under continuous ECG recording. RR interval series were analyzed using histogram distribution, split in 100ms-width classes, from 600ms to 1000ms. For each class, mean (MRR) and root-mean-squared difference (RMS) of consecutive normal RR intervals were calculated. Only pairs of consecutive RR intervals suiting a particular class were included. RMS was analyzed in the whole series (RMS-T), and in RR intervals pairs of AC (RMS-AC) and DC (RMS-DC) phases. Regression lines of RMS (T, AC, DC) vs. MRR were calculated, correlation coefficients tested, and angular coefficient compared between groups using Student t-test. RMS variables were log-transformed. ($\alpha < 0.05$)
Results: Correlation coefficient was significant for all regression lines ($p < 0.05$). Mean RMS-AC showed significant difference between groups. In HG, RMS-T, RMS-AC and RMS-DC significantly increased proportionally to MRR ($p < 0.05$). In CG, only RMS-AC showed significant increase as a function of MRR (Fig. 1).

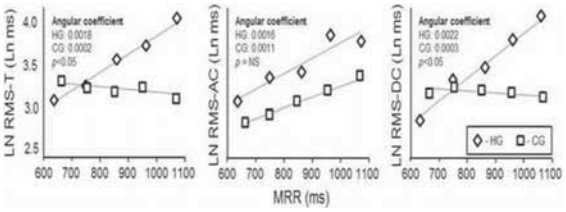

Figure 1. Regression lines of RMS vs MRR.

Conclusion: During HUTT, HRV increases proportionally to the mean RR interval in HG. This behavior is lost in the CG, particularly in DC phase, reflecting parasympathetic incompetence.

CARDIOVERSION AND ANTICOAGULATION IN ATRIAL FIBRILLATION

P6215 | BEDSIDE
Cardioversion of atrial fibrillation using dabigatran as thromboembolic prophylaxis

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Purpose: Cardioversion (DC cardioversion or pharmacological) of non-acute atrial fibrillation (AF) should be performed with preceding anticoagulation treatment, usually warfarin. An INR level between 2 and 3 during 3 to 4 weeks prior to cardioversion is usually requested. In practice, time to conversion is often delayed due to labile INR levels. With new oral anticoagulants (NOAC) the time to conversion can potentially be shortened. The safety of this strategy needs to be examined. Data from sub-group analysis from clinical trials with NOAC do not clarify whether 3 to 4 weeks' treatment with NOAC is sufficient to prevent thromboembolism (TE) after cardioversion. The aim of this prospective study was to assess the incidence of TE in patients converted during treatment with Dabigatran (D).
Method: We investigated the medical records of 436 patients from 4 hospitals where (D) had been used prior to cardioversion. TE within 30 days was the primary end point.
Results: 389 patients with persistent AF scheduled for DC cardioversion were included. The mean age was 64.6 years and 21.6% were women. The mean CHADSVASC score was 1.8. 93.6% of patients had (D) 150 mg b.i.d. Time from initiation of (D) treatment to cardioversion was 33 days. In 93.6% cardioversion resulted in sinus rhythm. During 30 days of follow-up 1 TE (0.26%) occurred.
Conclusion: In this prospective study from a clinical material, not part of a clinical trial, we found a low incidence of TE when (D) was used as TE prophylaxis in association with cardioversion. These results indicate that 4 weeks of (D) treatment seems to be a safe alternative strategy to warfarin during cardioversion in patients with AF.

P6216 | BENCH
Does cardioversion of atrial fibrillation improve cerebral blood flow?

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Purpose: Atrial fibrillation (AF) has been associated with cognitive impairment and we have recently shown that AF is associated with decreased brain volume independent of stroke in an elderly population. The causes may include multiple cerebral microemboli or hypoperfusion of the brain, but remain speculative. Previous data from our group have shown decreased cerebral blood flow in elderly patients with AF compared to those in sinus rhythm. The purpose of this study was to test the hypothesis that cerebral blood flow improves after direct current (DC) cardioversion for AF.
Methods: A prospective study involving patients undergoing elective DC cardioversion is ongoing at our institution. A magnetic resonance imaging (MRI) examination of the brain was performed immediately prior to DC cardioversion and repeated ten weeks later. Total cerebral blood flow was measured with phase contrast magnetic resonance imaging (PC-MRI) at the level of the skull base for direct flow measurements in the internal carotid arteries and basilar artery, providing the total sum of blood supply to the brain. In addition, we assessed brain perfusion

with arterial spin labeling magnetic resonance imaging (ASL-MRI). ASL-MRI has the advantage over PC-MRI of measuring perfusion directly in the brain tissue capillary network.
Results: Currently 36 patients have been enrolled with a mean age of 64.3±7.5 years. Preliminary results for those patients who have undergone MRI, both before cardioversion and after successful cardioversion and remained in sinus rhythm, show that total cerebral blood flow measured with PC-MRI increased from 574±112 ml/min to 710±177 ml/min after CV. Total brain perfusion by ASL-MRI increased from 41±11 ml/100g/min to 46±10 ml/100g/min and total grey matter perfusion measured by ASL-MRI increased from 44±11 ml/100g/min to 50±11 ml/100g/min. Correlation between blood flow measurements with ASL-MRI and PC-MRI was 0.84, $p<0.0001$.
Conclusions: These preliminary data suggest that total cerebral blood flow and brain perfusion may improve after DC cardioversion for AF. Reduced cerebral blood flow and diminished perfusion may be an underlying mechanism in decreased brain volume seen in elderly individuals with AF and thus potentially play a causative role in the cognitive impairment seen in this arrhythmia. Further studies are needed to investigate this possible relationship.

P6217 | BEDSIDE
Utility of HAS-BLED score in evaluating the risk of major bleeding and death in patients with non-valvular atrial fibrillation undergoing direct-current cardioversion

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Background: The HAS-BLED score is well validated to predict the risk of major bleeding in patients with non-valvular atrial fibrillation (NVAF). Its utility to predict bleeding events and death in NVAF patients undergoing direct-current cardioversion (DC-CV) is unknown. We studied the role of HAS-BLED score in predicting major-bleeding and death in real-world individuals with NVAF undergoing DC-CV.
Methods: Between January 2008 and June 2012, 571 consecutive DC-CV procedures were performed to 406 patients (70.1% male; mean age 66.4±11.2) with NVAF. In 540 procedures, HAS-BLED was calculated, and related to the incidence of major-bleeding and death.
Results: During a median follow-up of 668 (IQR: 293-1186) days, there were 21 major bleeds (3.7%) and 26 deaths (4.6%), being annual rates of major bleeding and death of 2.02% and 2.51%, respectively. Bleeding was gastrointestinal in 11 (52.4%), neurological in 5 (23.8%) and other site in 5 (23.8%). Aetiology of death was vascular (or probably vascular) in 13 (50.0%), non-vascular in 11 patients (42.3%) and unknown origin in 2 (7.7%). The HAS-BLED score was significantly associated with major bleeds (HR: 2.03, 95%CI: 1.53-2.68; $p<0.001$) and death (HR: 2.44, 95%CI: 1.83-3.25; $p<0.001$). HAS-BLED performed well in predicting both major bleeding (c-statistic: 0.77; 95%CI: 0.66-0.88; $p<0.001$) and death (c-statistic: 0.82; 95%CI: 0.74-0.91; $p<0.001$).

Annual rate of major-bleeding and death in relation with HAS-BLED score

HAS BLED score	Annual rate of major bleeding (%)	Annual rate of death (%)	Patients in category (n)
0	0	0	45
1	0.45	0	120
2	1.44	1.08	151
3	2.00	2.45	136
4	1.82	2.73	60
5	6.83	10.27	16
6	29.80	24.83	11
7	0	54.64	1

Conclusions: In patients with NVAF undergoing DC-CV, HAS-BLED score was a good predictor of the occurrence of both major-bleeding and death.

P6218

ABSTRACT WITHDRAWN

P6219 | BEDSIDE
Blood pressure increases after successful cardioversion for atrial fibrillation

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Background: Atrial fibrillation (AF) and high blood pressure (BP) are both common conditions that co-exist to a large extent. Despite this, knowledge about how AF influences BP and how rhythm control affects BP is scarce. Further, 24-hour ambulatory BP (ABPM) is a well documented method that enhances risk prediction but is less well studied in patients with AF.
Material and methods: We studied 25 patients with AF who were referred for electric cardioversion (EC). Office BP as well as ABPM were recorded shortly before (within 1 week) and shortly after (within 1 week) EC. 19 patients had complete ABPM-recordings and were included for this analysis. Out of these 19 patients, 7 patients had a quick return of AF after EC and consequently had AF during the BP-measurements post EC (group 1). 12 patients had a successful EC and were restored to sinus rhythm (group 2)
Results: In group 1 mean 24-hour systolic BP was non-significantly lower at the recording post EC but in group 2, mean 24-hour systolic BP significantly increased by 10 mm Hg ($p<0,01$). See table 1. One patient in group 2 had an increase of antihypertensive medication between the ABPM before and after EC. The remaining 11 patients had unchanged medication and thus changes in medication could not account for the difference in BP. The changes in systolic office BP before and after EC was statistically not significant.
Conclusion: Patients with successful EC to sinus rhythm had a marked increase of their 24-hour systolic BP in contrast to patients that were still in AF after unsuccessful EC. It is possible that we either underestimate the "true" BP in patients with AF or that the hemodynamic changes after restoration to sinus rhythm lead to an increase in BP. In both cases, this may have important implications for adequate management of BP in patients with AF. These findings should be replicated in a larger study and further studies should elucidate the possible mechanisms involved.

P6220 | BEDSIDE
Low incidence of intracardial thrombus formation by direct oral anticoagulants in the setting of electrical cardioversion

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Purpose: Data regarding the comparison of direct oral anticoagulants (DOAs)

Abstract P6219 – Table 1

	Age (years) (m±SD)	Males (%)	Treated high BP (%)	Office BP (syst) mm Hg before EC (m±SD)	Office BP (syst) mm Hg after EC (m±SD)	ABPM-syst 24-h mean mm Hg before EC (m±SD)	ABPM-syst 24-h mean mm Hg after EC (m±SD)
Group 1 (AF after EC) n=7	70±7	57	57	126±11	130±19	118±9	114±9
Group 2 (SR after EC) n=12	69±8	67	42	126±11	135±20	123±14	133±19*

*$p<0.01$ compared with ABPM before EC (repeated measures ANOVA).

with vitamin K antagonists (VKA) in the prevention of intracardial thrombusformation (ICT) in atrial fibrillation (AF) in the setting of electrical cardioversion (ECV) is sparse.
Methods: A total of 500 pts with indication for ECV were enrolled. 404 pts received a transesophageal echocardiography (TEE) to exclude ICT and to determine the left atrial appendage blood flow velocity (LAAV). 9 pts with a history of ICT were excluded. Endpoint was the TEE-guided detection of ICT and preformation.
Results: Endpoint was reached by 16 pts (4.1%). These pts showed a significant higher CHA2DS2-VASc score and lower LAAV. 2.28% of all pts with pos. ICT result were under VKA therapy, whereas only 0.51% received DOAs (p=0.011). Dabigatran and Rivaroxaban showed a significant diminished incidence of ICT compared with VKA (p=0.003).

Table 1

	Total	Pos. ICT	Neg. ICT	p-value
Patients (n), (%)	395 (100%)	16 (4.1%)	379 (95.9%)	–
Age, years	67.2±11.4	69.9±3	66.9±0,6	0.31
Male, %	278 (70.4%)	12 (75%)	266 (70.2%)	0.86
CHA_2DS_2-VASc score	2.9±1.6	4,0±0.3	2.8±0.1	<0.001
EHRA	2.3±0.7	2,5±0.7	2.3±0.04	0.19
INR	1.6±0.7	1,6±0.2	1.6±0.04	0.5
LAAV, m/s	0.4±0.2	0,18±0.03	0.41±0.01	<0.001
VKA, n (%)	139 (35.2%)	9 (56.3%)	130 (34.3%)	See text
Rivaroxaban, n (%)	117 (29.6%)	1 (6.3%)	116 (30.6%)	See text
Dabigatran, n (%)	36 (9.1%)	1 (6.3%)	35 (9.2%)	See text
Apixaban, n (%)	7 (1.8%)	0	7 (1.9%)	–
LMWH, n (%)	66 (16.7%)	3 (18.8%)	63 (16.6%)	–
ASA, n (%)	10 (2.5%)	0	10 (2.6%)	–
No OAC, n (%)	25 (6.3%)	2 (12.5%)	23 (6.1%)	–

Conclusions: The rate of new diagnosed ICT prior to ECV in pts managed with DOAs is significant lower than in pts with VKA therapy. DOAs potentially prevents from ICT more effectively than VKA.

P6221 | BEDSIDE
Dabigatran improves efficiency of an elective direct current cardioversion service

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Purpose: Direct current cardioversion (DCCV) is an effective method for treating atrial fibrillation. Anticoagulation prior to DCCV is mandatory to reduce the risk of thromboembolism. Historically, achieving and maintaining stable anticoagulation with Warfarin was challenging in some patients leading to high levels of procedure cancellations or rescheduling and long delays for DCCV. The recent introduction of novel oral anticoagulants such as Dabigatran offers a potential alternative to Warfarin therapy in this patient group. We aimed to examine the impact of the use of Dabigatran on our DCCV service as an alternative to Warfarin.
Methods: We analysed 242 DCCVs performed on 193 patients over a 36-month period. Patients were divided into 2 cohorts. Cohort A included cases in the 22-month period prior to the introduction of Dabigatran. Cohort B included cases in the 14-month period after the introduction of Dabigatran. Patients in the later cohort were treated either with Warfarin or Dabigatran 150mg twice daily. Rates of cancellation and rescheduling, time taken to DCCV and outcomes were compared between the two cohorts and between the two anticoagulants.
Results: All patients in cohort A received Warfarin. In cohort B, 48.4% received Dabigatran; the other patients were established and stable on Warfarin or had reasons for taking Warfarin (e.g. metal heart valve). The average CHA2DS2 VASc score for all patients was 2.08. A small number of patients (10%) were cancelled in both cohorts due to non-anticoagulation issues (e.g. patients' choice, referral for ablation and spontaneous return to sinus rhythm). A significantly larger number of patients from cohort A were rescheduled due to subtherapeutic INRs compared to cohort B (42% versus 15%, p<0.001). Those who received Dabigatran also had significantly lower rates of rescheduling compared to those who received Warfarin (9.7% versus 34.4%, p<0.001). The length of time between initial clinic assessment and DCCV was 22 days shorter in patients taking Dabigatran compared to Warfarin (45 versus 67 days; p=0.0015). Outcomes in achieving and maintaining sinus rhythm were comparable in both cohorts and anticoagulants (p>0.05).
Conclusions: Cancellations of DCCV appointments due to subtherapeutic INRs disrupt clinical care and the resulting inefficiency can escalate treatment cost. This study demonstrates that the use of Dabigatran instead of Warfarin in patients undergoing DCCV reduced rescheduling and thus improved efficiency.

P6222 | BENCH
Czech AF 2012 registry: profile of atrial fibrillation patients receiving antithrombotic therapy before noac

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Purpose: Profile of Czech AF 2012 registry is an epidemiological survey conducted by 197 Czech internal medicine and cardiology specialists who aimed to provide a comprehensive view of patients with non-valvular atrial fibrillation in the Czech Republic with respect to the prevention of stroke, before new anticoagulants were available.
Methods: It involved 982 patients, average age 69.9+10.04 years. The population of men was slightly higher (n=543, 55.3%), especially in the age group under 65 years; women prevailed in the age group above 75 years (55.7%).
Results: One quarter (25.1%) of patients was diagnosed with atrial fibrillation for less than 2 years; 23.2% for 2-5 years; 13.5% for 6-10 years, and 8.6% for more than 10 years. 20.7% of patients had paroxysmal atrial fibrillation; 58.5% indicated permanent atrial fibrillation, i.e. lasting more than one year. 58.7% of patients received medication regulating the heart rhythm; 44.0% had another antiarrhythmic medication. 13.8% of patients used their medication once a day; 55.1% twice a day, and 29.6% three times a day. 38.7% of patients were after cardioversion, 7.9% were after ablation. 91.5% of patients received warfarin alone or as dual (1.4%) therapy. Only 8.7% of patients had medium or severe kidney impairment. Only 7.5% of patients used acetylsalicylic acid, 0.2% used dual antiplatelet treatment.
Only 3.0% of patients had CHADS2=0; 55.8% were at a medium risk (CHADS2=1-2), and 41.2% at a high risk (CHADS2>2). 22.1% of patients had one associated condition; 27.5% had two associated conditions; 19.8% had three associated conditions; 28.7% had four or more associated conditions; and only 2.0% indicated no associated condition or gave no answer. The most common associated condition was hypertension (90.2%), followed by ischemic heart disease (50.9%) and diabetes mellitus (41.8%).
95 patients (9.7%) had a history of embolism while receiving antithrombotic therapy. 102 patients (10.4%) had a clinically significant bleeding event while on antithrombotic therapy, 51 patients needed hospitalization.
The average frequency of INR measurements was 10.2 per year (10.4 by cardiologists, 10.1 by internal medicine specialists). 61.6% INR mesurements were within the therapeutic range of 2-3. The dose of warfarin was changed in average 3.9x per year.
Conclusion: Atrial fibrillation patients are commonly elderly, polymorbid and high-risk patients on a pharmacological medication two to three times a day in more than 80% ! INR monitoring was close to the level described in large international studies, almost 2/3 of patients were within the therapeutic range.

P6223 | BEDSIDE
What factors determine the use of new oral anticoagulants in our country after the publication of the 2012 European Guidelines on atrial fibrillation - primary results of the 800 patient study

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Background: European guidelines are not always fully implemented into clinical practice, even though recommendations for the management of AF are based on strong evidence.
Aim: To describe the use of new oral anticoagulants (NOAC, dabigatran, rivaroxaban) in patients with non-valvular atrial fibrillation (AF) after the publication of the guidelines of the European Society of Cardiology in 2012.
Methods: We analysed 839 consecutive patients with AF who were hospitalized between 2012 and 2014 in our reference cardiology university. We performed a multivariable analysis on factors which are associated with the use of NOAC.
Results: 195 (23%, mean age 71+12 years) patients out of 839 were treated with NOAC, 410 (52%) with anti-vitamin K agents, 111 (14%) with ASA and 81 (10%) had no treatment. Clinical type of AF was reported to be paroxysmal in 310 (37%), persistent in 173 (21%) and permanent in 327 (39%) patients. CHA2DS2VASc score in analyzed population (839 patients) was 2,6±1,5 and HAS-BLED was 1,6±1,0; in NOAC population (194 patients): CHA2DS2VASc score was 3.2±1,7 and HAS-BLED - 1.2±0,9.
In logistic regression negative predictive factors for the treatment with NOAC were: age >65 years (OR 0.28, p<0.001, 95% CI 0.20-0.40), continuous type of AF (OR 0.51, p<0.001, 95% CI 0.36-0.73), higher risk of bleeding (HAS-BLED≥3) (OR 0.36, p=0.001, 95% CI 0.20-0.65), presence of heart failure (OR 0.60, p=0.003, 95% CI 0.43-0.84) and anaemia (OR 0.60, p=0.01, 95% CI 0.41-0.88). Of all patients, 39 (32%) received reduced dose of NOAC. In logistic regression positive predictive factors for reduced dose of NOAC were eGFR<50ml/min. (OR 6.09; p<0.001, 95% CI, 2.73-13.57), age >80 years (OR 12.77; p<0.001, 95% CI, 5.75-28.40), higher risk of bleeding (HAS-BLED≥3) (OR 10.91, p<0.001, 95%CI, 2.95-30.46) and anaemia (OR 4.11 p<0.001, 95%CI, 2.02-8.37).
Conclusion: The management of AF patients in our country in 2012-2014 has relatively well adapted to guideline recommendations but it is not optimal. Oral anticoagulant therapy with VKA (majority) or NOACs are given to 76% of eligible patients, including those at risk for bleeding. Elderly population and those with long-lasting continuous AF, despite higher risk of stroke and bleeding, were given NOAC less frequently than younger patients with paroxysmal AF.

P6224 | BEDSIDE

New onset AF is strongly associated with underuse of anticoagulation in Chinese patients with atrial fibrillation: analysis of CRAF study

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Background: Warfarin was underused in Chinese patients with atrial fibrillation (AF), which has been improved but still low compared to Europe. While, the reasons of underuse of warfarin may be not the same as before. The purpose of this study was to identify the factors related to suboptimal use of anticoagulant in mainland China.
Methods: The China Registry of AF (CRAF) is a multicenter, cross-sectional study with 4,161 patients with atrial fibrillation enrolled from 111 tier 2 and 3 hospitals from Jul to Dec 2012. In this analysis, all the patients were divided into anticoagulant group and control group. Multivariate logistic regression analysis was used to identify the independent risk factors for the patients without anticoagulant treatment.
Results: In this cohort, 85.6% of the patients were non-valvular atrial fibrillation (NVAF). 2211 were male (53.1%) and the mean age was 68.3±11.9 years. The mean CHADS2 score for 3551 NVAF patients was 1.83±1.40, with 53.0% had a score ≥2. The mean CHA2DS2-VASc score was 3.03±1.85 and 76.6% had a score ≥2. There were more patients prescribed warfarin in patients with valvular AF compared to patients with NVAF (57.3% vs 25.6%, p<0.0001). Multivariate logistic regression model showed that the independent risk factors associated with the patients not receiving anticoagulant were older age, nonvavular AF, new onset AF, high DBP, not receiving any antiarrythmia treatment and no history of stroke. The most significant factor associated with patients not taking warfarin was new onset AF (Table 1).

Table 1. Independent risk factors associated with patients without anticoagulation treatment

	OR	95%CI	p value
Age	1.26	1.17; 1.35	<0.0001
NVAF	3.07	2.50; 3.78	<0.0001
New onset AF	4.52	3.14; 6.50	<0.0001
No antiarrythmia treatment	3.10	2.16; 4.45	<0.0001
DBP	1.01	1.01; 1.02	0.0001
Without history of stroke	1.60	1.32; 1.95	<0.0001
History of bleeding	2.88	2.23; 3.73	<0.0001

Conclusions: This study suggested there was a big gap between daily practice and guidelines regarding the stroke prevention in patients with new onset AF in China.

P6225 | BEDSIDE

Effect of ventricular rate on the outcome of cardioversion in patients with acute atrial fibrillation. The FinCV Study

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Purpose: There is no previous data on the effect of ventricular rate (VR) prior to cardioversion (CV) on the outcome of CV in acute atrial fibrillation (AF).
Methods: The FinCV Study collected data on 7397 CVs performed in patients with acute AF in 3 centers. For this analysis, the patients were divided into 3 groups based on VR of AF: low (<60/min), moderate (60-140/min) and high (>140/min).
Results: AF episodes with high VR were more common in women, caused more often chest pain or hemodynamic instability, were more often the first episode or an episode started within 12 hours (Table). VR had no effect on the success of CV or the occurrence of asystole or bradycardia (<40/min) after CV, but early recurrences were more infrequent in patients with high VR.

	VR<60 n (%)	60≤VR≤140 n (%)	VR>140 n (%)	p value
N	94	6350	953	
Age, yr	60.7±12.3	62.4±12.2	60.5±12.6	<0.001
Female gender	22 (23.4)	2264 (35.7)	410 (43.0)	<0.001
First AF episode	26 (27.7)	1411 (22.2)	321 (33.7)	<0.001
Prior AF <30 days	20 (21.3)	1081 (17.0)	122 (12.8)	0.002
Duration of AF episode <12 hours	34 (36.2)	2873 (45.2)	533 (55.9)	<0.001
Angina or hemodynamic instability	5 (5.4)	586 (9.2)	173 (18.1)	<0.001
Asystole or bradycardia	0 (0)	75 (1.2)	7 (0.7)	NS
Success of CV	90 (95.7)	6000 (94.5)	897 (94.1)	NS
Recurrence of AF <30 days	17 (18.1)	1125 (17.7)	112 (11.8)	<0.001

Conclusions: Low VR does not predict bradycardic complications after CV of acute AF, but is related to early recurrences.

P6226 | BEDSIDE

Survey of general practitioners on the actual conditions of atrial fibrillation treatment, including anticoagulation therapy

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Background: Recently, novel oral anticoagulation drugs have been put on the market and prescriptions of anticoagulation drugs for atrial fibrillation (AF) are increasing more than before. However, the details of those prescriptions are unknown.
Methods: We did a nationwide survey on the treatment of AF and anticoagulant therapy in May 2013. There were 16 questions and 505 (28%) of 1,800 replied.
Results: Fifteen percent of the doctors specialized in cardiology and the remaining 85% specialized in primary care or other fields. There were no regional differences in the response rate. Almost all the general practitioners (98%) had experience with consulting AF patients. Further, 71% of those doctors continued to consult those patients at their own institute instead of sending them to the local hospital. Most importantly, 88% of the practitioners had prescribed oral anticoagulants for AF patients. In particular, warfarin had been prescribed to most of the patients (79%). However, 40% of the institutes still selected and prescribed antiplatelet therapies. In addition, 55% of the doctors experienced strokes and 70% of the doctors experienced heart failure caused by AF. Fifty-five percent of all doctors experienced bleeding complications and 59% of them were gastrointestinal bleeding.
Conclusion: Our survey demonstrated the tendency for general practitioners to prescribe anticoagulant therapy for AF patients more than before.

ANTICOAGULANTS IN ATRIAL FIBRILLATION

P6228 | BEDSIDE

Optimal international normalized ratio in warfarin therapy in Korean patients with non-valvular atrial fibrillation

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Purpose: Optimal international normalized ratio (INR) in elderly atrial fibrillation (AF) patients with a higher rate of hemorrhagic event risk remains unclear. We investigated the efficacy and safety of low-intensity warfarin therapy (target INR 1.6-2.6) in elderly Korean patients with nonvalvular AF.
Methods: We enrolled 528 NVAF patients (mean age 67±9; 361 men) taking warfarin. Annual rate of ischemic stroke, systemic embolism and major bleeding requiring blood transfusion or hospitalization time to therapeutic range (TTR) was 50±20% for all patients. Ischemic stroke and systemic embolism occurred in 20 patients with INR 1.00-2.44 (16 ischemic strokes and 4 systemic embolisms) and major bleeding in 37 patients with INR 1.74-no coagulation (7 intracranial hemorrhages, 21 gastrointestinal bleedings, and 9 others). Incidence rates of ischemic or hemorrhagic event at INR <2.00, 2-3, and >3 were 3.0%, 1.4%, and 20.1%/year, respectively. In patients with age ≥70 years, CHADS2, CHA2DS2VASc and HAS-BLED score were significantly higher than in those with age <70 years. When we applied INR between 1.6 and 2.6 recommended by Asia pacific heart rhythm society AF guideline in patients with age ≥70 years, TTR was increased 47.5% to 65.2%. Also ischemic or hemorrhagic event rate within TTR was decreased 1.9% to 1.2% (Figure).

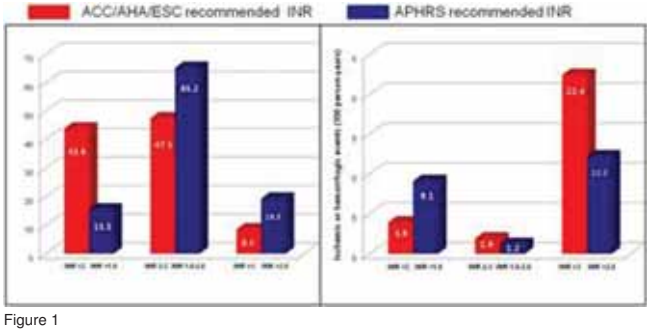

Figure 1

Conclusions: The low-intensity warfarin therapy (INR 1.6-2.6) should be considered in elderly patients with NVAF.

P6229 | BENCH
The FIRST registry: Comparison of anticoagulant treatment in patients with atrial fibrillation

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Aim: The FIRST registry aimed to compare patients with atrial fibrillation (AF) treated by direct thrombin inhibitor dabigatran or warfarin.
Methods: The study was performed in 10 centres enrolling 190 patients treated with dabigatran and 146 patients treated with warfarin.
Results: The patients did not differ in age (71.7+10.3 resp. 73.0+10.2 years). Upon enrolment, 33.2% and 35.6% of patients showed sinus rhythm. The AF was classified as paroxysmal in 30.5 resp 30.9%, persistent 16.8 resp. 19.5%, permanent 27.4 resp. 34.9% and in 25.3 resp. 14.8% the date were not available (all ns). The most frequent concomitant disease was hypertension (81.1% resp. 80.5%), diabetes mellitus (28.4% resp. 26.8%) and heart failure (28.4= resp 24.8%) (all ns). The last dose of warfarin before changing over to dabigatran was significantly higher than the maintenance dose in patients treated with warfarin 6.4+4.3 mg vs. 4.6 + 3.2 mg ($p<0.001$). The accompanying medication did not differ, the most frequently prescribed drugs were ACE inhibitors/ARBs 76.3% rep. 72.5% and beta blockers 76.3% resp 74.5% (all ns). The patients did not differ in the risk according to CHA2DS2-VASc; 53.1% and 52.4% respectively, showed a score above 4. The principal difference was in the HAS BLED score: 55.3% of patients treated with dabigatran demonstrated a score of three or more while only 33.5% of those treated with warfarin did ($p<0.001$). In 14.7% of patients treated with dabigatran, serious bleeding was observed during the previous treatment with warfarin. while with respect to patients treated with warfarin serious bleeding occurred in only 2.0%. The most frequent reason (56.6%) for changing over to dabigatran was the impossibility to maintain INR within the therapeutic range. The average period of treatment with dabigatran was 2.67+1.57 months. Only two non serious bleedings on dabigatran appeared during this period.
Conclusion: Patients are transferred from warfarin to dabigatran in particular due to the impossibility to maintain INR within the therapeutic range. Data from the first 190 patients show that no selection occurred, that dabigatran is administered to a typical population with non-valvular atrial fibrillation and with an average to higher risk of thromboembolic accident (CHA2DS2-VASc score of 2–5) but with a relatively high bleeding risk (HAS BLED >3) in the absolute majority of patients. Nevertheless, the incidence of minor bleeding over an average of three months is less than 1% of patients; no serious bleeding occurred.

P6230 | BEDSIDE
Antithrombotic treatment of atrial fibrillation in general practice: application of the GRASP-AF audit tool

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Purpose: Despite compelling evidence of the efficacy of oral anticoagulation (OAC) for stroke prevention in atrial fibrillation (AF) not all suitable patients receive appropriate antithrombotic therapy. We examined the utilization of antithrombotic therapy in AF patients in general practice, based on the computerized GRASP-AF (Guidance on Risk Assessment and Stroke Prevention in Atrial Fibrillation) audit tool available for UK general practitioners to assess stroke risk and antithrombotic therapy use.
Methods: 2259 AF patients [mean (SD) age 76 (12) years, 46% female, represent 2.15% of the total general practice population] identified by the GRASP-AF tool from 11 general practices were followed-up for 12 months.
Results: Most patients were moderate-high risk of stroke (92.5% based on the CHA2DS2-VASc score of $\geq$1 if male, $\geq$2 if female; 86% based on CHADS2 score $\geq$1). Only 1080 (48%) patients received OAC and 921 (41%) received antiplatelet agents. OAC was declined by 113 (5.0%) patients and contraindicated in 187 (8.3%). Based on CHADS2, OAC (± antiplatelets) was prescribed to 51% of patients at moderate-high risk of stroke; with CHA2DS2-VASc, OAC was prescribed to 50% of moderate-high risk patients, and approximately 28% of low risk patients (Table). Over a 12 month period, 67 (3.0%) developed stroke, including 5 (0.2%) hemorrhagic strokes. Use of antiplatelet agents was associated with a significantly increased risk of stroke on univariate analysis (odds ratio 1.88, 95% CI 1.14-3.09, $p<0.016$).

Antithrombotic therapy and stroke risk

	None	Antiplatelet agents	OAC	OAC + antiplatelet agents
$CHADS_2$ score				
Low risk	126 (39%)	108 (33%)	80 (25%)	11 (3%)
Moderate-high risk	240 (12%)	704 (36%)	891 (46%)	98 (5%)
CHA_2 DS_2 -VASc score				
Low risk (0 if male, 1 if female)	86 (51%)	38 (22%)	40 (24%)	6 (4%)
Moderate-high risk	281 (13%)	774 (37%)	931 (45%)	103 (5%)

Conclusion: OAC therapy in AF remains suboptimal in the UK general practice settings, with sub-optimal treatment of high-risk patients and inappropriate OAC use in low-risk patients. Aspirin monotherapy use remained excessive in high-risk patients, despite exposing such patients to an increased risk of stroke.

P6231 | BEDSIDE
Left atrial sphericity improves CHADS2 score stroke prediction in patients with atrial fibrillation

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Introduction: Left atrial sphericity (LASP) is a new remodeling parameter that has independent predictive value for atrial fibrillation (AF) recurrence after AF ablation. We sought to evaluate whether LASP adds prognostic information to CHADS2 score and LA appendage (LAA) characteristics.
Methods: Twenty-nine patients with history of prior stroke and 29 age- and gender-matched controls were included. All patients underwent cardiac MRI prior to the AF ablation procedure. LASP was calculated using a 3D left atrial (LA) reconstruction that excluded pulmonary veins and the LAA. Manual LAA segmentation was used to calculate the volume. LAA morphology was classified as previously reported: chicken wing, cauliflower, windsock, and cactus. Area under the ROC curve (AUC) was calculated for LASP, LA volume, LAA volume and CHAD score (Stroke2 excluded). A cut-off value was determined for optimal stroke prediction.
Results: Mean age of the study population was 61±11 years, 79.3% were male, 53.4% had hypertension, and 8.6% had diabetes. Compared to controls, patients with history of prior stroke had significantly higher LASP (80.2±3.1 vs 82.5±3.3, p=0.008); there were no differences in CHAD score (0.66±0.76 vs 0.90±0.86, p=0.26), LA volume (95±31 vs 94±25ml, p=0.97), LAA volume (5.9±2.9 vs 5.5±2.9, p=0.66), or LAA morphology (p=0.514). LASP had the only significant ROC curve for stroke prediction (AUC 0.706 [0.571-0.842], p=0.007). The CHAD score had an AUC of 0.58 (0.432-0.728, p=0.297), LA volume of 0.497 (0.345-0.649, p=969), and LAA volume of 0.463 (0.312-0.613, p=0.624). The best cut-off value for LASP was 83.6% (52% sensitivity, 90% specificity). A significantly greater proportion of patients with high LA sphericity (>83.6%) had prior stroke (83.3% vs 35.0% below the cut-off; P=0.001). Logistic regression showed predictive value for LASP (OR 1.26 per each 1% increase [1.85-52.20], P=0.013), but not for CHAD score (OR 1.457 [0.755-2.81]; p=0.262). The combination of both parameters (CHAD-LASP) increased the predictive value over CHAD score alone (AUC of 0.719 [0.585-0.852], p=0.004).
Conclusion: LA sphericity is associated with history of prior stroke in patients undergoing AF ablation and increases the predictive value over CHAD score alone.

P6232 | BEDSIDE
Dabigatran discontinuation in "real-world" practice among Chinese population

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Objectives: Dabigatran is an oral direct thrombin inhibitor for stroke prophylaxis in patients with non-valvular atrial fibrillation (AF). While it serves as an appealing alternative to warfarin, its use is limited by adverse effects such as bleeding and dyspepsia. Our observational study aimed to describe dabigatran discontinuation rate and possible predictors in real-world practice.
Method: Chinese patients receiving dabigatran were identified from our hospital registry of AF. Data pertaining to AF, demographics, cardiovascular risk factors, and medications were collected from clinical records. The primary outcome was permanent discontinuation of dabigatran. Reasons of discontinuation were retrieved from the medical records and discharge summaries. Cox proportional hazards models were used to evaluate the association between baseline characteristics and drug discontinuation.
Results: A total of 467 patients were identified, of whom 248 (53.8%) were males. The mean age was 73 years and the mean CHA2DS2-Vasc score was 3.58. Over a mean follow-up period of 16 months, 101 patients (21.6%) permanently discontinued dabigatran with the mean time-to-discontinuation of 8 months. The major reason of discontinuation was dyspepsia (30.7%), followed by other side effects (13.9%). The next commonest reason was patient-driven factors (11.9%), including concerns about dosing frequency (5.9%), side effects (4.0%), laboratory monitoring (1.0%) and cost (1.0%). Lower baseline estimated glomerular filtration rate, absence of hypertension, prior use of proton-pump inhibitor and H2-receptor antagonist were independent predictors of drug discontinuation. Rates of ischemic stroke, intracranial bleeding and major gastrointestinal bleeding were 1.54%, 0.51% and 4.11%/person-year respectively.
Conclusion: Dabigatran discontinuation is common among Chinese patients. Our observations highlight the challenges in the use of dabigatran in real-world setting and the importance of doctor-patient communication before initiation of a possible life-long, self-financing medication.

P6233 | BEDSIDE
Profile and outcome of anticoagulated patients admitted to the emergency department of a tertiary hospital for bleeding complications

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Purpose: Advance age and comorbidity are known risk factors for bleeding in patients taking oral anticoagulants (OAC). The aim of this study was to describe the profile of patients with bleeding events seen in our emergency department (ED) and to identify factors associated with major bleeding (MB).
Methods: We included patients receiving OAC for non-valvular atrial fibrillation (NVAF) or mechanical prosthesis (MP) who were admitted to the ED for bleeding events from June 2012 to January 2014. MB was defined as a reduction in Hb level ≥20 gr/L, requirement of ≥2 units of packed red cells, requirement of invasive procedures, or bleeding in a critical site. All other bleeding episodes were considered minor (mB). Age, performance of activities of daily living (Barthel), comorbidity (Charlson), comedications, and HASBLED score were recorded.
Results: 73 patients (57% men) were seen in the ED for bleeding complications. 66 patients received vitamin K antagonists (VKA) for NVAF (56 patients) or MP (10 patients) and 7 patients received dabigatran (all for NVAF). Bleeding sites were: intracranial (IC) (13), gastrointestinal (40), urine tract (9), lung or airway (3), others (8). MB occurred in 44 patients (91% required admission for a mean of 11±9 days) and 29 patients had mB. There were not significant differences between patients with MB and mB in terms of age (80±9 vs 78±8), Barthel index (88±22 vs 88±25), and Charlson index (2±1.9 vs 1.8±1.5). 22% of patients were taking antiplatelet agents and 8% NSAID, but there were not significant differences between patients with MB or mB regarding the use of these drugs. In patients receiving VKA, there were not significant differences between patients with MB and mB neither in terms of INR level (4.2±2.4 vs 3.8±2.3) nor in the percentage of patients with INR within therapeutic range (INR 2-3 for NVAF and 2.5-3.5 for MP). The HASBLED score did not show significant differences between patients with MB or mB (2.6±0.9 vs 2.9±1.2). IC bleeding was the cause of death in 4 patients. In 50% of patients with IC bleeding the INR was above the therapeutic range but only in 25% the INR was ≥4. HASBLED was ≥3 in a 38% of patients with IC bleeding.
Conclusions: In this study, the severity of bleeding was not related to comorbidity or to a higher bleeding risk profile. IC bleeding, the most serious complication of anticoagulation, was neither related to a higher HASBLED score nor to the intensity of the anticoagulation. One limitation of the study is the small number of patients included. More studies are needed to define which patients are at a higher risk of MB while taking OAC.

P6234 | BEDSIDE
Left atrial appendage thrombus in the modern anticoagulant era

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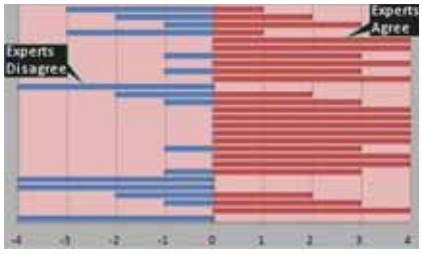
Background: Transesophageal echocardiography (TOE) guided direct current cardioversion (DCCV) following variable duration anticoagulation has become the modern standard of care for many patients with atrial fibrillation. Agents used include warfarin, heparins, and more recently dabigatran and rivaroxaban. During a single anaesthetic, if left atrial appendage (LAA) thrombus is excluded by TOE, the patient is cardioverted. Historical TOE data from the 1990's prior to routine anticoagulation for cardioversion suggested LAA thrombus rates of approximately 14%. Whilst new anticoagulant agents have been safely used for TOE-guided DCCV, rates of LAA thrombus precluding DCCV in the modern era have not been reported.
Methods: Data from 640 patients listed for TOE/DCCV with therapeutic anticoagulation of variable duration were reviewed. All cases where thrombus was identified and DCCV deferred had independent blinded retrospective review by four senior TOE cardiologists (compressed stored DICOM data).
Results: LAA thrombus causing cancellation of DCCV was identified in 34/640 patients (5.3%) -23/34 standard warfarin/heparin, 9/34 with dabigatran and 2/34 with Rivaroxaban. Retrospective interobserver variability amongst experts agreed only to a moderate extent as to the presence of LAA thrombus (binary scale "more likely present" vs "more likely absent"), kappa = 0.46, P<0.00005.



Conclusions: LAA thrombus remains surprisingly highly prevalent in anticoagulated patients scheduled for DCCV in the modern era. Operator risk aversion regarding "missing a clot" (false negative) with potential catastrophic clinical repercussions (stroke etc), led to relatively high inter-observer variability (with a tendency to excess false positive studies) compared to retrospective expert review.

P6235 | BEDSIDE
CHA2DS2-VASc as a predictive score system for the clinical outcomes in acute myocardial infarction patients with atrial fibrillation

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Purpose: CHA2DS2-VASc score system has been used in the assessment for the development of stroke in patients with atrial fibrillation (AF). Substantial patients with AF experience acute myocardial infarction (AMI). However, little is known about the prognostic impact of CHA2DS2-VASc score system on the clinical outcomes in AMI patients with AF.
Methods: We analyzed a total of 1,021 patients (71.0±12.0 years old, 693 males) AMI with AF enrolled in Korean AMI Registry (KAMIR). In-hospital outcome was defined as in-hospital mortality and complications including death, major- or minor-bleeding, and new onset cerebrovascular accidents (CVA). One-year clinical outcomes were analyzed according to CHA2DS2-VASc score in a linear correlation method, and defined as the composite of major adverse cardiac events (MACEs) including death, myocardial infarction (MI), target vessel revascularization (TVR) and coronary artery bypass graft (CABG). CHADS2, CHA2DS2-VASc, TIMI risk score were calculated and the predictive accuracy for one-year mortality and major adverse cardiac events (MACEs) of them were analyzed by Receiver Operation Characteristics Curve.
Results: Patients with one year MACEs had significantly higher CHADS2 (2.5±1.4 vs. 1.8±1.3, p<0.001), CHA2DS2-VASc (3.6±1.7 vs. 2.6±1.7, p<0.001), and TIMI risk score (ST segment elevation MI 7.0±2.6 vs. 4.9±2.5, p<0.001; non ST segment elevation MI 3.6±1.1 vs. 3.1±1.1, p<0.001) than the patients without one year MACEs. In-hospital mortality was higher in patients with CHA2DS2-VASc≥4 (13.1% vs. 6.4%, p<0.001) without differences in the rate of CVA, major bleeding, and new onset heart failure. Both one year mortality (linear p<0.001) and the composite of MACEs (linear p<0.001) were increased as stepwise manner according to CHA2DS2-VASc score. The predictive accuracy of CHA2DS2-VASc score was better for one year mortality (area under curve (AUC) 0.715, 95% confidence interval 0.67-0.76, p<0.001) than CHADS2 (AUC 0.674) and TIMI score (AUC 0.712). Also, the predictive accuracy of CHA2DS2-VASc score was better for one year MACEs (AUC 0.671, 95% confidence interval 0.63-0.72, p<0.001) than CHADS2 (AUC 0.651) and TIMI score (AUC 0.664).
Conclusions: CHA2DS2-VASc score can provide simplicity with accuracy for the prediction and risk stratification of one year mortality and MACEs as well as in hospital mortality in AMI patients with AF. CHA2DS2-VASc score could be utilized for the prediction of both clinical outcomes and stroke in AMI patients with AF.

P6236 | BEDSIDE
Why are oral anticoagulants restrained from patients with atrial fibrillation - outcome of a population based assessment in a geographically well-defined catchment area

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Purpose: Atrial fibrillation (AF) affects about 3% of the adult western population and incurs an annual stroke risk of 5%. Use of oral anticoagulants (OAC) significantly reduces this risk. As only about 50% of patients with AF in Europe are prescribed OAC, an opinion of "inappropriate underutilization" has been set. Little is known about why AF patients are not prescribed OAC more frequent in routine clinical management. The aim of this study was to assess this issue in a geographically well-defined population.
Methods: The FNH-registry records all identified patients with AF in a catchment area of 65532 people. Of the 1616 patients with an identified AF on December 31 2010, 588 (36%) were not prescribed OAC. The physicians (n=22) responsible for their treatment were identified, and requested to complete a standardised questionnaire to assess the reason of restraining OAC in each individual case.
Results: This analysis is based on the 520 first returned questionnaires. The

Table 1. Reasons of restraining OAC in patients with $CHADS_2$ 0, 1 and ≥2

	$CHADS_2$=0	$CHADS_2$=1	$CHADS_2$ ≥2
Number of patients (n)	88	152	280
No medical indication (%)	75.0	44.7	0.7
Bleeding (%)	2.2	8.6	15.7
Side effects of OAC/interaction (%)	1.1	0.7	2.2
Poor compliance (%)	3.4	10.5	13.9
Repeated falls (%)	0.0	3.3	10.7
Patient decline OAC treatment (%)	0.0	7.2	7.5
Converted to sinus rhythm (%)	9.1	6.6	5.0
Malignancy (%)	1.1	2.6	1.8
Severely declined general condition (%)	2.3	7.2	21.1
Other specified reason (%)	4.5	3.9	6.8
No reason identified (%)	1.1	4.6	14.6

given reasons of restraining OAC in patients with CHADS2 0, 1 and ≥2, respectively, are given in Table 1.
Conclusion: This is, to our knowledge, the first study to assess causes of restraining OAC in a geographically well-defined population, thus including hospital- as well as non-hospital based healthcare. In patients with CHADS2≥2 the main causes of restraining OAC were severely declined general condition, a history of bleeding and poor compliance.

P6237 | BEDSIDE
Prognostic impact of CHA2DS2Vasc and renal impairment in non valvular atrial fibrillation patients: which is the best equation to stratify the risk of future events?

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Purpose: Renal dysfunction (RD) is associated with an increased risk of thromboembolic (TE) and haemorrhagic (HE) events in non valvular atrial fibrillation (NVAF). Which method of RD evaluation can better stratify the risk of cardiovascular (CV) events in NVAF is still unknown. We evaluated the additive prognostic role of RD in a "real world" population of NVAF outpatients.
Methods: Between 2009 and 2013, we enrolled 3399 consecutive NVAF patients (pts). Clinical data were derived from the E-data chart for outpatient clinic of our cardiovascular center. In 1509 pts glomerular filtration rate (GFR) was available at first clinic evaluation with Cochkroft-Gault (CG), Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology collaboration (CKD-EPI) equations. Renal dysfunction was defined as GFR <60ml/min. We recalculated CHA2DS2VASc score, adding 1 point for RD using all equations. The median follow-up was 27 months (IR 15-40). We evaluated incidence of death, CV hospitalization (CVH), TE and major HE.
Results: The mean age was 75 years (IR 68-81), 39.7% were male; 1217 (80.1%) pts had hypertension, 466 (30.8%) diabetes mellitus, 295 (19.5%) heart failure, 196 (13%) prior stroke or transient ischemic attack and 23 (1.5%) previous bleedings. Median GFR was 61.8mL/min (IR 47-77) with CG, 72.4 (IR 59-87) with MDRD and 69.1 (IR 55-84) with CKD-EPI. Median HAS-BLED score was 3 (IR 2-4) and ≥3 in 70% of the pts; median CHA2DS2VASc score was 4 (IR 3-5) and ≥2 points in 91.1% pts. 623 (41%) pts were on anticoagulant therapy (OAT). During follow-up we recorded 531 (35%) deaths or CVH, 113 (7.5%) TE and 24 (1.6%) major HE. Adding 1 point for RD to CHA2DS2VASc score pts were reclassified in a worse-class of risk in 47% with CG, 34% with CKD-EPI and 27% with MDRD (p<0.001). Pts with combined TE/HE during follow-up were reclassified by the presence of RD in a worst class of risk in 62% with CG, 46% with CKD-EPI and 35% with MDRD (p=0.009). Stratifying these pts by OAT, CG and CKD EPI reclassification were associated to a significant higher risk of TE/HE (p=0.006) only in not OAT pts; conversely MDRD identified an higher risk only in OAT pts (p=0.04). Adding RD (1 point) to CHA2DS2VASc score considering pts that experienced death/CVH, 58.5%, 44.7% and 36.4% of pts with RD were reclassified in a worst class of risk with CG, CKD-EPI and MDRD respectively (p<0.001), independently from OAT.
Conclusions: In NVAF pts the risk reclassification by CHA2DS2VASc and RD shows an additive predictive prognostic impact. CG was the best formula to reclassify pts risk of events.

P6238 | BEDSIDE
Do we use new oral anticoagulants in patients with non-valvular atrial fibrillation according to the renal function?

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Background: According to the ESC guidelines for the management of atrial fibrillation (AF) new oral anticoagulants (NOAC, dabigatran, rivaroxaban) are not recommended in patients with severe renal impairment (CrCl<30 mL/min).
Methods: We analysed 839 consecutive patients with AF who were hospitalized between 2012 and 2014 in our reference cardiology university centre. We investigated whether NOAC were used according to the renal function defined by KDIGO 2012.
Results: Out of 839 patients 194 (23%, mean age 70±11 years) were prescribed NOAC. CHA2DS2VASc score in the whole population (839 patients) was 2,6±1,5 and HAS-BLED was 1,6±1,0. In NOAC population CHA2DS2VASc score was 3.2±1,7 and HAS-BLED - 1.2±0,9. Chronic kidney disease was present in 31 (16%) patients. Mean eGFR evaluated by Cockroft-Gault (C-G) formula was 82 ml/min./1,73m^2, by MDRD formula 72 ml/min./1,73m^2 and by CKD-EPI 69 ml/min./1,73m^2.
Out of 194 patients on NOAC: 3,0% had severely impaired eGFR, 26%, and 52% had moderate and mild impairment, respectively, while 19% had normal eGFR. Patients with moderately and severely decreased eGFR (<60ml/min./1,73m^2) tended to be older (p<0.001), they were more frequently females (p=0.045) and had more often permanent AF (p=0.004), heart failure (p=0.039), higher CHA2DS2-VASc score and HAS-BLED scale (p<0.001, p=0.01, respectively) and more frequently used reduced dose of NOAC (p<0.001).
All patients (n=55) with eGFR<60ml/min/1,73m^2 had CHA2DS2VASc score ≥2 and 10.9% (n=6) from this group had HAS-BLED scale ≥3.
According to the C-G and MDRD formula there were 3% of the patients with eGFR <30 ml/min./1,73m^2, and there were 3,5% of the patients according to CKD-EPI equation who were given NOAC. HAS-BLED scale in patients with eGFR<30 ml/min./1,73m^2 was >3. All patients were prescribed reduced dose of rivaroxaban.
Conclusions: Anticoagulation treatments with NOAC remain suboptimal in patients with AF and moderate or severe renal impairment. About 3% of the patients with severe renal failure are given NOAC despite guideline recommendations. The risk of stroke, as measured by the CHA2DS2-VASc score, was associated with decreased renal function. Also the risk of bleeding, as assessed by HAS-BLED scale, correlated with renal impairment.

P6239 | BEDSIDE
High-sensitivity cardiac troponin T levels do not increase after elective, biphasic, direct-current cardioversion for atrial fibrillation/flutter

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Background: The kinetics of high-sensitive cardiac troponin T (hs-cTnT) levels after elective, biphasic, direct-current cardioversion for persistent atrial fibrillation/flutter remains unknown.
Methods: We examined hs-cTnT kinetics in 24 patients at baseline and at 2, 6, and 24 hours post-cardioversion, and again at 7 and 30 days. We also examined levels of creatine kinase, aspartate aminotransferase, lactate dehygrogenase, brain natriuretic peptide (BNP) and high-sensitive C-reactive protein (hs-CRP).
Results: The cardioversion procedure was successful in all of the patients, and 70% of the patients remained in sinus rhythm at 30 days following cardioversion. Mean baseline hs-cTnT concentration was 21.7±12.7 ng/L with 14 patients presenting with levels above the detection level (13 ng/L). hs-cTnT levels did not change significantly over time although they tended to decrease by 30 days (16.6±6.1 ng/L). There was no significant rise in other markers of myocardial injury. Similarly, BNP and hs-CRP levels were elevated at baseline and tended to decrease over time.
Conclusions: Patients with persistent atrial fibrillation/flutter have elevated hs-cTnT levels, as part of a general rise in biomarkers, such as BNP and hs-CRP, without a further rise after cardioversion. After cardioversion, there is a gradual, nonsignificant decrease in levels of these biomarkers over time.

ANTICOAGULANTS AND STROKE IN ATRIAL FIBRILLATION

P6241 | BENCH
Relationship between deteriorating renal function and adverse events in atrial fibrillation patients using novel oral anticoagulants

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Introduction: Renal function is crucial to use novel oral anticoagulants (NOAC) in patients with non-valvular atrial fibrillation (NVAF).
Methods and results: This study consists of 689 NVAF patients (68±11 years old) receiving NOAC (dabigatran: 442, rivaroxaban: 217, apixaban 30 patients) in our hospital. The mean estimated creatinine clearance (eCCr) before NOAC was 74±26 ml/min. The eCCr <50ml/min was present in 113 of 689 (16%). The eCCr was measured again in the remaining 576 patients with eCCr ≥50 ml/min before NOAC, and eCCr fell into <50 ml/min in 27 patients (3.9%) at 295±250 days after NOAC (Table). Adverse events were observed in 39 of 113 patients (35%) with eCCr <50ml/min before NOAC, 12 of 27 patients (44%) with eCCr fall <50 ml/min after NOAC, and 121 of 549 patients (22%) with preserved eCCr ≥50 ml/min after NOAC. Major bleeding was observed in 2 of 113 patients (2%) of eCCr <50ml/min before NOAC, 2 of 27 patients (7%) of eCCr fall <50 ml/min

	Patients with eCCr fall <50 ml/min	Patients with preserved eCCr ≥50 ml/min	P value
Patients number	27	549	
Age, years old	76±9	65±11	<0.0001
Sex, n (M/F)	16/11	411/138	0.08
Serum Cr (mg/dl) at baseline	0.87±0.20	0.83±0.17	ns
eCCr (ml/min) at baseline	56±5	82±23	<0.0001
Previous stroke or TIA, n (%)	7 (26)	60 (11)	0.02
Congestive heart failure, n (%)	11 (41)	109 (20)	0.009
Hypertension, n (%)	16 (59)	306 (56)	ns
Diabetes mellitus, n (%)	3 (11)	77 (14)	ns
CHADS2 score, mean	2.3±1.3	1.3±1.1	<0.0001
CHA2DS2-VASc score, mean	3.8±1.4	2.2±1.5	<0.0001
Thromboembolic event, n (%)	1 (4)	4 (0.7)	ns
Adverse event, n (%)	12 (44)	121 (22)	0.007
Major bleeding, n (%)	2 (7)	0 (0)	< 0.0001

after NOAC. On the other hand, no major bleeding event was observed in patients with preserved CCr ≥50 ml/min after NOAC.
Conclusion: Deteriorating renal function is associated with increasing adverse events. Repeated measurement during NOAC is important to avoid adverse effects.

P6242 | BEDSIDE
Characterizing patients who do not do well on a vitamin-K antagonist therapy in a community based cohort of patients with non valvular atrial fibrillation

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Background and aim: In atrial fibrillation (AF) the risk of complications increases when INR (International normalized ratio) values are out of therapeutic range. Mean time in therapeutic range (TTR) below 60% indicates that vitamin-K antagonist (VKA) is inefficient. We aimed to determine TTR values in patients who were on VKA treatment and had non-valvular AF and to identify the factors affecting TTR in these patients.
Method: Retrospectively, between June 2012 and December 2013, 534 consecutive patients with non-valvular AF who were attending the out-patient Cardiology clinics of a tertiary hospital were enrolled. For the purpose of the present study, only patients who were on uninterrupted AVK in at least >12 months and had more than 9 consecutives INR values were included. TTR values were determined using the fraction of INR's in range (the number of INR's within target range [2 to 3] divided by the total number of INR's). A cut off value of 60% was used to assess efficiency of TTR. Thereafter, patients were classified into two groups according to their TTR values (≥60% vs. <60%) and the characteristic features of these groups were compared. Independent predictors of having TTR <60% were identified using a binary logistic regression analysis.
Results: The mean age of the patients was 73±11 years and 40.4% were female. 64% of the patients had 15 INR's consecutive tests, and the average number of INR's tests was 13.9±1.8. Mean TTR value was 59±16%, and 44.8% (n=239) had TTR values below 60%. In the univariate analysis, patients with TTR <60% were younger (72±12 vs. 74±11 years; p=0.03) and more commonly women (65% vs. 34%; p=0.01) than those patients with TTR ≥60%. History of congestive heart failure, chronic obstructive pulmonary disease, moderate with alcohol consumption, being on home amiodarone, hyperuricemia, and a history of prior malignant disease, were significantly associated (p<0.05) with TTR <60%. Prior coronary artery disease and smoking status showed a tendency to be associated with TTR <60% (p<0.10). After a multivariate adjustment, the independent predictor of having a TTR <60%, were moderate alcoholism consumption (odds ratio 5.3 [95%CI 1.1-24.8]), history of malignant disease (odds ratio 2 [95%CI 1.2-4.0]), on home amiodarone (odds ratio 1.6 [95%CI 1.1-3.1]), and age <65 years (odds ratio 1.5 [95%CI 1.1-1.8]).
Conclusions: We found that about 45% of our study patients had inefficient TTR values and that TTR values were associated with some potentially modifiable factors such as alcohol consumption and amiodarone treatment.

P6243 | BEDSIDE
Cost-effectiveness of non-Vitamin-K oral anticoagulants compared to warfarin in patients with non-valvular atrial fibrillation

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Non-Vitamin-K antagonist oral anticoagulants (NOAC) demonstrated in edoxaban's ENGAGE-AF trial, apixaban's ARISTOTLE trial, rivaroxaban's ROCKET-AF trial and dabigatran's RE-LY study non-inferiority or superiority for the prevention of the primary endpoint of stroke and systemic embolic events, for occurrence of severe bleeding complications and mortality in patients with non-valvular atrial fibrillation (NVAF) compared to warfarin adjusted to an INR (international normalized ratio) of 2 to 3. The pharmacoeconomic aspects of dabigatran, rivaroxaban and apixaban demonstrated to be cost effective in many countries for the health care system mainly. Here we determined the cost-effectiveness of 60mg od and 30mg od edoxaban from a German payers perspective and compared the results with those obtained for the approved NOAC.
We used the Markov decision model to analyse the quality adjusted life years (QALY), total costs (one time costs for events, rehabilitation costs for inpatient and ambulatory care, inpatient medical treatment costs, daily costs for drugs) and incremental cost effectiveness ratio (ICER) based on the data of the ENGAGE-AF study. The results were compared with data previously derived from the RE-LY, ROCKET-AF and ARISTOTLE trials under a German health care insurance perspective.
The base-case analyses of a 65 years old person with a CHADS2 score >1 gained 0.17 and 0.21 QALY over warfarin for 30mg od and 60mg od edoxaban, respectively. The ICER was 50.000 and 68.000 Euro per QALY for the higher and lower dose of edoxaban based on the results of the Monte Carlo Simulation (MCS). The results of the one-way sensitivity analysis showed that the costs for edoxaban (both doses), the quality of life utilities, the treatment of ischemic stroke and of major and intracerebral bleeding complications were important values in our model. The various willingness-to-pay thresholds were analysed by using the probabilistic sensitivity analysis (PSA) in the MCS by varying all variables simultaneously. Edoxaban 60mg od and 30mg od were cost-effective at willingness-to-pay threshold of 52.000€ per QALY and 67.000€ per QALY. The results for apixaban were in between the 2 edoxaban doses and higher for dabigatran both doses and rivaroxaban.
Edoxaban in addition to apixaban may be regarded as the most cost-effective DOAC from a German public health care insurance perspective. The larger reduction in medical cost was mainly driven by reductions in the risks major bleeding events. Additional real life use of NOAC has to substantiate the present results for specific countries.

P6244 | BEDSIDE
An analysis of net clinical benefit of new oral anticoagulants versus warfarin in atrial fibrillation phase III trials

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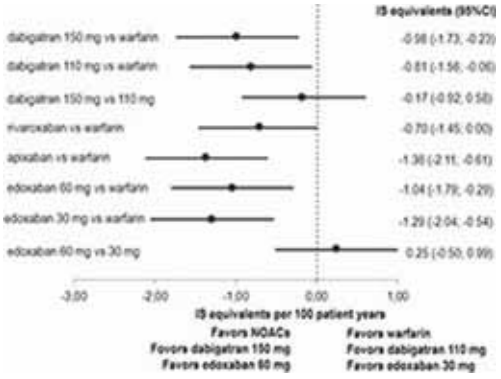
Purpose: We estimated the net clinical benefit (NCB) of new oral anticoagulants (NOACs) vs warfarin across phase III clinical trials, evaluating composites of efficacy and safety in patients with non-valvular atrial fibrillation (AF).
Methods: We considered the incidence rates (IR) per 100 patients years for all-cause mortality, ischemic stroke, systemic embolism, hemorrhagic stroke, adjusted major bleeding (major bleeding minus hemorrhagic stroke) and myocardial infarction for each treatment. We first calculated the Rate Ratio (RR) of NOACs vs warfarin for a composite outcome (CO) of such events. We then attributed to each event a weight according to its reported impact on death, as derived from previous studies. Ischemic stroke (IS) was used as the reference value. The NCB was defined as the weighted sum of IRs for each NOAC (dabigatran 150mg and 110mg, rivaroxaban 20mg, apixaban 5mg, edoxaban 60mg and 30mg) minus the weighted sum of IRs in the respective comparator (warfarin). NCB was expressed as IS equivalents prevented per 100 patients years of treatment.
Results: Expressed as RR, 95%CI, the CO was significantly lower than warfarin for 150mg dabigatran (0.91, 0.79-0.99), apixaban (0.82, 0.73-0.89), and both 60mg and 30mg edoxaban (0.89, 0.79-0.96; 0.83, 0.73-0.89). There was a favourable, but not significant, trend for better NCB vs warfarin as to 110mg dabigatran (0.92, 0.80-1.00) and rivaroxaban (0.93, 0.82-1.01). According to weighted NCB estimates, IS equivalents were significantly lower for all NOACs compared with warfarin (Figure). There were no significant differences in CO and NCB between the two doses of dabigatran and edoxaban.



Conclusions: Considering a weighted NCB, all NOACs showed a better compounded efficacy/safety profile than warfarin in patients with AF.

P6245 | BEDSIDE
High risk of stroke during 3 years among survivors from acute myocardial infarction who had atrial fibrillation during the acute phase of AMI

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Aim: The aim of the analysis was to compare 3-year clinical outcomes of survivors from AMI who had or not AF during the acute phase of AMI.
Methods: We used the Polish Registry of Acute Coronary Syndromes (PL-ACS) database (for baseline characteristics of AMI patients from year 2009) linked to the database from the only health insurer in Poland (National Health Fund) for follow-up data on cardiovascular events up to 3 years following the index MI.
Results: From 25738 patients with AMI (49% NSTEMI and 51% STEMI), 1688 (6.7%) had FA during index hospitalization. In-hospital mortality was higher in patients with FA (14.4% vs 6.3%, p<0.0001). Among 23455 survivors, 1445 (6.1%) were those with FA during AMI. The baseline clinical characteristics shows that

Abstract P6245 – Table 1

	No FA	FA	P value		No FA	FA	P value
Number of patients (%)	22010 (93.9%)	1445 (6.1%)		Procedures during 3 years:			
Rehospitalizations for cardiovascular reasons during 3 years:	56.0	65.7	<0.0001	– Blood transfusion, %	8.0	10.9	0.0001
– Myocardial infarction, %	10.8	11.8	0.21	– PCI, %	23.5	16.5	<0.0001
– Unstable angina, %	10.8	7.8	0.0003	– CABG, %	7.0	4.7	0.0008
– Stable angina, %	40.0	29.6	<0.0001	– Peacemaker, %	1.6	4.4	<0.0001
– Atrial fibrillation, %	2.4	10.7	<0.0001	Mortality after discharge:			
– Heart failure, %	11.5	29.1	<0.0001	– 30-day, %	1.2	2.8	<0.0001
– Stroke, %	2.9	9.8	<0.0001	– 1-year, %	7.4	19.1	<0.0001
– Life threatening arrhythmias, %	1.5	2.5	0.0050	– 3-year, %	15.2	37.3	<0.0001

they were patients of the higher risk profile: older (mean age 73.7 vs. 65.0, $p<0.0001$), more frequently with the history of hypertension (77% vs. 70%), diabetes mellitus (34% vs. 24%), ischemic heart diseases (25% vs. 14%), previous MI (21% vs. 15%), heart failure (19% vs. 6%), and stroke (8% vs. 3%). They were also less frequently treated invasively (PCI in 52% vs. 73% in patients without FA). The follow-up data concerning rehospitalization, cardiac procedures and mortality up to 3 year following index MI are shown in the table. Significantly more patients with FA were hospitalized due to stroke (9.8% vs. 2.9% in patients without FA, $p<0.0001$).

Conclusion: Survivors of AMI who had FA during the acute phase are patients of high initial risk profile and higher long-term mortality and morbidity. Every 10th patient with FA in AMI is hospitalized due to stroke during 3 years following MI.

P6246 | BEDSIDE

Truly low-risk patients with newly diagnosed non-valvular atrial fibrillation at risk of stroke: 1-year outcomes from the GARFIELD Registry

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Purpose: To study 1-year outcomes in truly low-risk patients with non-valvular atrial fibrillation (AF).
Methods: In the ongoing, international registry, GARFIELD, a total of 12,458 prospective patients with AF were enrolled at 739 sites in 30 countries between March 2010 and January 2013. Results are reported at 1-year follow-up. CHADS2 and CHA2DS2-VASc scores were calculated in 12,195 and 12,184 patients, respectively.
Results: A total of 6.6% and 3.6% of patients had CHADS2 and CHA2DS2-VASc scores of 0, respectively ("low-risk"). Low-risk patients were younger and more likely to be male. Approximately 75% of these patients received antithrombotic or antiplatelet therapy. The unadjusted 1-year incidence of all-cause death, stroke/systemic embolism (SE) and major bleeding increased substantially when risk scores were $\geq$1. The 1-year incidence of stroke/SE was lower in those with CHA2DS2-VASc of 0 vs CHADS2 of 0 (0.7% vs 1.2%).

Table 1

	$CHADS_2$ = 0 (n=797/12,195)*	CHA_2 DS_2-VASc = 0 (n=435/12,184)†	$CHADS_2$ = 0 and CHA_2 DS_2-VASc = 0 vs $CHADS_2$ ≥1 and CHA_2 DS_2-VASc ≥1, HR (95% CI)‡
VKA	228 (28.6)	113 (26.0)	–
VKA+AP	58 (7.3)	28 (6.4)	–
FXa or DTI	60 (7.5)	26 (6.0)	–
FXa or DTI +AP	17 (2.1)	7 (1.6)	–
AP	252 (31.6)	136 (31.3)	–
No antithrombotic therapy	182 (22.8)	125 (28.7)	–
1-year outcomes (unadjusted)	(n=807/12,195)	(n=440/12,184)	
All-cause death, n %	25 (3.1)	14 (3.2)	0.582 (0.343–0.989)
Stroke/SE, n %	10 (1.2)	3 (0.7)	0.435 (0.139–1.362)
Major bleeding, n %	1 (0.1)	1 (0.2)	–

*Data missing for 10 patients. †Data missing for 5 patients. AP, antiplatelet; DTI, direct thrombin inhibitor; FXa, direct Factor Xa inhibitor; VKA, vitamin K antagonist.

Conclusion: A minority of patients with non-valvular AF are classified as truly low-risk, and continue to receive antithrombotic therapy. A trend towards differences in predictive accuracy for stroke/SE between CHADS2 and CHA2DS2-VASc scores was apparent.

P6247 | BEDSIDE

Prevalence of intracardiac thrombus in patients with atrial fibrillation or flutter treated with new oral anticoagulants versus vitamin K antagonists

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Purpose: New oral anticoagulants (NOACs) are increasingly used as an alternative to vitamin K antagonists (VKAs) for stroke prevention in patients with non-valvular atrial fibrillation (AF). Despite large anticoagulation trials there are still under-explored aspects that affect the daily management of patients on this medication. Specifically, data concerning the safety of cardioversion under NOAC therapy are limited. The aim of this study was to assess the prevalence of intracardiac thrombus formation during NOAC treatment in comparison to VKAs.
Methods: A total of 150 patients with non-valvular AF or atrial flutter subjected to transesophageal echocardiography (TEE) while on anticoagulation therapy with NOACs (rivaroxaban (R), n=64; dabigatran (D), n=29) or VKAs (phenprocoumon (P), n=57) were included between 07/2012 and 06/2013.
Results: Baseline characteristics (age, body mass index, left atrial diameter) did not differ significantly between anticoagulant groups. Study patients exhibited median CHA2DS2-VASc scores of 4 (P) and 3 (R, D) and a median HAS-BLED score of 1 (P, R, D), respectively. Intracardiac thrombi were detected in 6/57 patients (10.5%) treated with VKAs. In comparison, we found thrombus formation in 4/64 (6.3%; R) and 1/29 (3.5%; D) patients treated with NOACs. In a subgroup analysis, patients under phenprocoumon with international normalized ratio <2 and patients treated with NOACs who had been on the respective medication for less than 3 weeks were excluded. In these groups thrombus rates yielded 13.0% (6/45; P), 5.4% (3/56; R), and 4.0% (1/25; D). Differences between anticoagulant groups were not statistically significant.
Conclusions: Intracardiac thrombi are frequently detected in a selected cohort of patients with AF receiving oral anticoagulation. The apparent tendency towards lower thrombus rates during NOAC treatment compared to VKA requires validation in larger patient cohorts. The data confirm the significance of TEE to rule out thrombi and extend our understanding of benefits and risks of NOACs in the setting of cardioversion.

P6248 | BEDSIDE

Cost-effectiveness of apixaban compared to edoxaban for stroke prevention in non-valvular atrial fibrillation

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Purpose: The European Society of Cardiology guidelines recommend consideration of novel oral anticoagulants (NOACs) including dabigatran, rivaroxaban and apixaban instead of warfarin for stroke prevention in non-valvular atrial fibrillation (NVAF) patients. Several published economic evaluations have deemed apixaban to be the most cost effective drug amongst the current anticoagulants. Edoxaban may be the 4th NOAC to the market based on recently published ENGAGE-AF trial. Limited data exists about its relative economic value versus apixaban. We assessed the cost-effectiveness of apixaban 5 mg BID versus edoxaban 60 mg or 30 mg QD as intended starting dose strategies for stroke prevention in NVAF patients, from a UK NHS perspective.
Methods: A Markov model was developed to evaluate the lifetime clinical and economic impact of apixaban 5mg twice daily versus edoxaban (30mg and 60mg once daily) in NVAF patients. A pair-wise indirect treatment comparison was conducted for the following end-points: ischemic stroke, systemic embolism, intracranial hemorrhage, other major bleeds, clinically-relevant non major bleeds, myocardial infarction and treatment discontinuations. Price parity was assumed between apixaban and edoxaban. Outcomes estimated over life-time horizon were healthcare costs, life years gained, and quality-adjusted life years (QALY) gained.
Results: Apixaban was predicted to increase life expectancy and QALYs versus low dose and high dose edoxaban over a lifetime horizon. These gains were achieved at cost-savings versus low dose edoxaban, thus dominating it in the analysis. Apixaban was cost effective versus edoxaban 60 mg QD with incremental cost effectiveness ratio (ICER) of £6,763/QALY gained, well below commonly

Cost-effectiveness of apixaban versus edoxaban

Comparator	Δ Costs in GBP (Apixaban – Edoxaban)	Δ QALYs (Apixaban – Edoxaban)	ICER (cost/QALY) Apixaban vs. Edoxaban
Edoxaban 30mg	–£48	0.073	Dominant
Edoxaban 60mg	£248	0.037	£6,763

accepted threshold of £20,000/QALY. One-way and probabilistic sensitivity analyses indicated that cost-effectiveness implications were robust over a wide range of inputs.

Conclusions: Among anticoagulation strategies for stroke prevention in NVAF patients, apixaban appeared to be a cost-effective alternative to high dose of edoxaban and was dominant against low dose edoxaban by providing greater effectiveness at lower costs.

P6249 | BEDSIDE
Predictors for detection of atrial fibrillation in cryptogenic stroke patients: insights from insertable cardiac monitor data in the CRYSTAL AF study

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Purpose: Undiagnosed atrial fibrillation (AF) may be responsible for a significant proportion of cryptogenic strokes (CS). However, the clinical, electrographic, and echocardiographic factors associated with the occurrence of AF in CS patients are not well understood. We assessed these factors in CS patients who received an insertable cardiac monitor (ICM, Reveal XT) for arrhythmia surveillance in the CRYSTAL AF study.

Methods: ICM patients ≥40 years old with CS or transient ischemic attack within 90 days prior to enrollment were studied. We assessed whether age, gender, race, body mass index, type and severity of index ischemic event, CHADS2 score, PR-interval, and the presence of diabetes, hypertension, congestive heart failure, or PFO predicted AF detection within the initial 12 months of follow-up using univariate and multivariable Cox proportional hazards models and receiver operator characteristic (ROC) curves.

Results: Among 221 ICM recipients (age 61.6±11.4 years, 64% male), adjudicated episodes of AF were detected in 29 patients within 12 months. In univariate analysis, significant predictors of AF included age >65 years (HR 2.8 [95% confidence interval 1.3-5.8], $p<0.01$), CHADS2 score (HR 1.9 per one point [1.3-2.8], $p<0.01$), PR interval (HR 1.3 per 10ms [1.2-1.4], $p<0.0001$), and diabetes (HR 2.3 [1.0-5.2], $p<0.05$). In multivariable analysis, age >65 (HR 2.5 [1.2-5.2], $p<0.05$) and PR interval (HR 1.3 [1.2-1.4], $p<0.0001$) remained significant and together yielded an area under the ROC curve of 0.73 (95% confidence interval 0.64-0.83).

Conclusion: Age >65 years and a longer PR interval at enrollment were independently associated with an increased propensity for AF in CS patients, however they offered only moderate predictive ability in determining which CS patients had AF detected by the ICM in the CRYSTAL AF study.

P6250 | BEDSIDE
Quality of Life and patient satisfaction data in atrial fibrillation patients stably treated with a VKA vs patients switched from a VKA to NOAC. The PREFER in AF registry

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The new direct oral anticoagulants (NOACs) are gradually being introduced in Europe for stroke prevention in non-valvular atrial fibrillation. Because of the non-requirement of coagulation monitoring, no food interactions and fewer drug interactions they promise to be better accepted by the patients, improving their quality of life (QoL). Whether patient-related issues actually affect the switch to anticoagulation using a NOAC has not been studied. In the PREFER in AF Registry, QoL and patient satisfaction questionnaires (EQ-5D-5L and/or PACT-Q2) were compared in patients stably treated with a VKA for ≥6 months (n=2102) vs those with a recent (within the past 12 months) switch from a VKA to a NOAC (n=213). Compared with patients stably treated with a VKA, patients switched from VKA to NOAC had similar age (72.4±9.1 vs 71.6±9.4 years), gender (60.9% vs 64.8% male patients) and BMI (28.2±5.1 vs 28.1±5.0). The following risk factors were more prevalent in the stably treated VKA patients compared with the switched patients: Arterial hypertension (76.2% vs 68.1%, P=0.0066), concomitant use of antiplatelet agents (20.1% vs 12.2%, P=0.0055) and heart valve dysfunction (39.7% vs 30.0%, P=0.0038). No significant differences were seen in other factors. As to the 25 features investigated by the QoL questionnaires, switched patients more often had mobility problems (13.3% vs 7.3%, P=0.0025); complained about severe difficulties in dose adjustments (9.8% vs 5.4%, P=0.0116); referred extreme discomfort about bruising or pain (8.5% vs 5.1%, P=0.0429); and were more often dissatisfied with the previous anticoagulant treatment (9.1% vs 5.3%, P=0.0266). These patients also less frequently reported to be non-anxious or depressed (77.2% vs 85.9%, P=0.009).

Mobility problems, complain about dose adjustments, discomfort about bruising or pain, dissatisfaction about OA treatment and some anxiety/depression traits appear to be related – and may possibly influence - the choice of switching from a VKA to a NOAC.

STROKE AND ANTICOAGULANTS IN ATRIAL FIBRILLATION

P6252 | BEDSIDE
Relationship between R2CHADS2 score and prophylactic efficacy during antiarrhythmic drugs therapy in Japanese patients with paroxysmal atrial fibrillation

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Background: R2CHADS2 score is a useful scheme for risk stratification of thromboembolism, whereas there has been little information in its usefulness for the evaluation of antiarrhythmic drugs therapy (AAD). This study included 505 paroxysmal atrial fibrillation (AF) patients (341 men, mean age 66±12 years, mean follow-up 51±39 months) and prophylactic efficacy was analyzed on the basis of R2CHADS2 score. AF recurrence was defined as the first ECG-documented AF episode during AAD, and permanent AF was defined as AF refractory to AAD or electrical cardioversion in which sinus rhythms could not be maintained for more than 6 months.

Results: (1) Survival rates free from AF recurrence at 1,3,6 and 12 months during AAD were 90%,77%,73% and 63% in score-0 group (N=155), 91%,82%,73% and 62% in score-1 group (N=140), 83%,74%,61% and 55% in score-2 group (N=76), 85%,70%,64% and 53% in score-3 group (N=66), and 84%,73%,60% and 44% in score-4 group (N=45), and 83%,65%,57% and 39% in ≥score-5 group (N=23), respectively (P=0.011, among 6 groups). (2) Survival rates free from progression to permanent AF at 12,36,60 and 90 months despite AAD were 95%,91%,86% and 92% in score-0 group, 96%,91%,89% and 88% in score-1 group, 95%,91%,86% and 82% in score-2 group, 95%,83%,80% and 77% in score-3 group, and 93%,91%,84% and 82% in score-4 group, and 87%,70%,57% and 43% in ≥score-5 group, respectively ($P<0.001$, among 6 groups). (3) In a multivariate logistic regression analysis adjusted for the potentially confounding variables, R2CHADS2 score was associated with AF recurrence (odds ratio [OR] 1.21, 95% confidence interval [CI] 1.05-1.40, P=0.008), and progression to permanent AF despite AAD (OR 1.33, 95% CI 1.67-2.49, $P<0.001$).

Conclusion: R2CHADS2 score is a useful scheme not only for risk stratification of thromboembolism but also for outcome of AAD in Japanese patients with paroxysmal AF.

P6253 | BEDSIDE
Left atrial appendage closure as an alternative to oral antikoaguation in high risk patients: a single-center experience

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Purpose: Atrial fibrillation (AF) is the most common heart rhythm disorder of the elderly and responsible for about 25% of all strokes. The annual stroke risk of patients with nonvalvular AF is about 5%. This can be reduced to approx. 1-1.5% p.a. by administration of oral anticoagulation (OAC). However, OAC hold a relevant bleeding risk (about 3-4% p.a.) Previous studies on left atrial appendage closure have shown an equivalent efficiency in reducing embolic events. So far, a combination of OAC and ASA 100mg is recommended for at least 3-6 months after implantation.

Methods and results: From 2-2012 to 01-2014 a percutaneous closure device of the LAA (LAA-occluder) was implanted under TEE guidance and general anesthesia in 90 consecutive patients with AF and complications under OAC. These patients received a dual antiplatelet inhibition (ASA 100mg/Clopidogrel 75mg) for 6 months without further OAC and thereafter ASA 100mg.

Of the 90 patients in the study (age 78±7), 50% were women; the avg. CHA2DS2-VASc score and HAS-BLED-score were 4.7 and 2.8. 8 patients (8.8%) had suffered from previous strokes. The most common indication for LAA closure was recurrent gastrointestinal bleeding with OAC (33%). In 83/90 (92%) patients a device was successfully implanted. 3 patients had a previously undetected LAA thrombus in the main LAA-lobe. In 4 patients the procedure was stopped due to unfavorable LAA-morphology (i.e. ≤15mm depth/width).
Overall 83 devices of all sizes were implanted (10x21mm/22x24mm/22x27mm/19x30mm/10x33mm). As periprocedural complications, one pseudoaneurysm and one AV-fistula of the A. femoralis sup. occurred. One patient developed a reactive polyserositis 10 days after the implantation which resolved after bilateral thoraco- and pericardiocentesis (non-hemorrhagical aspirate). No other implantation related complications did occur. 45 patients received a TEE control after 2-3 months. There were no device dislocation/protrusion and no relevant peridevice flow in color-doppler echo (all <3mm). In one case (1.1%) we found an asymptomatic thrombus centered on the LAA-device (spherical, approx 17x18mm), which completely resolved after 3 months of OAC and did not recur.
Conclusions: In a real-world scenario percutaneous LAA-closure can be safely and effectively used as alternative to OAC. In our high-risk group of elderly patients with atrial fibrillation, dual platelet inhibition can be used directly instead of OAC after implantation. To ensure a good result and detect device-related thrombus, TEE monitoring should be recommended to all patients after about 2-3 months.

P6254 | BEDSIDE
Status of anticoagulation therapy and incidence of events in Japanese elderly patients with non-valvular atrial fibrillation: a repot from the J-RHYTHM Registry

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Background: Although novel oral anticoagulants (NOACs) have been available for anticoagulation therapy in patients with non-valvular atrial fibrillation (NVAF), usage of NOACs has been limited in elderly patients due to lack of evidence of its safety. Warfarin has been still widely used in real-world clinical situation and is the most reliable anticoagulant especially in very old patients with aged ≥85 years. However, there is little information about the status of anticoagulation therapy in very old NVAF patients.
Aim: To elucidate the status of anticoagulation therapy and to clarify the incidence of events in elderly NVAF patients using the data from the J-RHYTHM Registry, a multicenter, nationwide, prospective, observational study.
Method: Consecutive series of all type AF patients were enrolled from 158 institutions. Of whole 7,937 patients, 7,406 NAVF patients (men 70.8%, 69.8±10.0 years) were eligible for analysis and divided into 3 age groups; <70 years (group Y: 3,365 patients), 70–84 years (group O: 3,711 patient), and ≥85 years (group VO: 330 patients) for comparison of baseline characteristics and incidence of events in different international normalized ratio (INR) levels (<1.6, 1.6–1.99, 2.0–2.59, 2.6–2.99, and ≥3.0). Patients were followed for 2 years or until an event of endpoint occurred. In case of any event, an INR value at the event was recorded.
Results: In groups O and VO, frequencies of female, persistent AF, hypertension, coronary artery disease, and mean CAHDS2 score (1.2±1.0, 2.0±1.2, and 2.7±1.2, P<0.001 for trend) were higher than in group Y. Rate of warfarin treatment in group VO (79.7%) was lower than in groups Y (83.9%) and O (89.4%). Achieving rate of the target INR level of 1.6–2.6 was lower in groups VO (57.8%) than in groups Y (65.1%) and O (66.7%). During a 2-year follow-up period, rates of both thromboembolism (0.9%, 1.9%, and 3.8%) and major hemorrhage (1.4%, 2.5%, and 3.4%) in patients with warfarin in 3 groups increased depending on age (P<0.001 for trend). Rates of both events in each INR level at the event in group VO (8.5%, 0%, 2.9%, 4.8%, and 12.5%, P=0.067, and 1.4%, 0%, 2.9%, 9.5%, and 37.5%, P<0.001, respectively) were higher than those in groups Y and O, and their trends were similar among 3 groups.
Conclusions: Frequency of warfarin treatment in Japanese NAVF patients aged ≥85 years was relatively high, though it was lower than in younger patients. According to the cumulative event rate in each INR level, an INR level of 1.6–2.0 might be the most safe to avoid hemorrhagic complications and effective at preventing thromboembolism in very old patients.

P6255 | BEDSIDE
Impact of newer oral anticoagulants Versus warfarin on cardioversions in atrial fibrillation

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Background: Patients with atrial fibrillation (AF) greater than 48 hours are anticoagulated prior to cardioversion, this can reduce the incidence of thromboembolization during peri-cardioversion period.
From clinical experience and time in therapeutic range (TTR) studies on warfarin that maintaining INR between 2 to 3 can be achieved in 63 - 76% of patients on a consistent basis, this leads to delay in cardioversion and prolonging time in AF. It affects patient's quality of life & adds cost to the healthcare system.
Methods: Between March 2012 to September 2013, 187 patients undergoing elective direct current cardioversion (DCCV) at Beaumont Hospital, were enrolled in the study. Medical charts and cardioversion records were analyzed. The CHADSVASC score and anticoagulants of every patient were recorded. Any bleeding issues, and thrombo-embolic complications peri DCCV were noted. We calculated delays and determined the reasons for same.
Results: 187 patients had DCCV performed, 41 on Rivoroxaban, 27 on Dabigatran. In total 68 patients were on NOAC versus 119 on Warfarin. 3 (4.4%) were delayed in Newer Oral Anticoagulants (NOAC) group (2 Non compliant, 1 medical illness) as compared to 31 (26%) of patients in warfarin group (28 patients had sub therapeutic INRs also had TOE findings of pre-thrombus formation in LAA, 3 had medical illness).
Average time interval between referral and DCCV for NOAC was 111.73 days and for warfarin 133.61 days. Patients that were delayed in warfarin group had average time interval between their cancellation and subsequent cardioversion was 120.5 days. The cost of cancellation of an elective DCCV and subsequent visits to warfarin clinic was estimated at approximately 1160€ per patient to the healthcare system.
Conclusions: Patients undergoing elective cardioversion on NOAC had better quality of life, less hospital visits and were less likely to be delayed or cancelled and also reduced cost to healthcare service as compared to patients on warfarin.

P6256 | BEDSIDE
International normalized ratio control and 1-year outcomes in patients with newly diagnosed atrial fibrillation: the GARFIELD Registry

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Purpose: To investigate frequency in range (FIR) of international normalized ratio (INR) measurements in relation to demographics, care settings and outcomes after 1 year in patients taking vitamin K antagonists (VKAs) for newly diagnosed non-valvular atrial fibrillation (AF).
Methods: In total, 6305 of 12,458 prospective patients were treated with VKAs at 1-year follow-up in the GARFIELD Registry, and INRs were available for 5115 VKA-treated patients. In this analysis, the target INR range was defined as 2.0–3.0, and the cut-off for poorly controlled INR was FIR <70% and for well controlled INR was FIR ≥70%.
Results: Age and gender did not have a significant influence on FIR, whereas increasing alcohol use and worsening chronic kidney disease were associated with lower FIR. Overall, only 25% of VKA-treated patients had FIR ≥70%. Compared with other settings, a greater proportion of patients (35%) treated at an anticoagulation clinic or thrombosis centre had FIR ≥70%. Unadjusted rates of death, stroke/systemic embolism, and major bleeding at 1-year follow-up were significantly higher in patients with FIR <70% than those with FIR ≥70%.

Variable	FIR <70% (N=3813)	FIR ≥70% (N=1302)	P-value
Ethnicity, non-Asian/Asian, %	72.4/85.6	28.6/14.4	<0.001
Alcohol use, light/moderate/heavy, %	72.8/79.6/86.8	27.2/20.4/13.2	0.001
Chronic kidney disease, II–III/IV–V, %	75.7/87.8	24.3/12.2	0.003
Previous stroke/transient ischaemic attack, %	69.1	30.9	<0.001
Clinical care setting at diagnosis, n (%)			<0.001
Hospital (n=2907)	2184 (75.1)	723 (24.9)	
Office (n=1303)	932 (71.5)	371 (28.5)	
Anticoagulation clinic/thrombosis centre (n=138)	90 (65.2)	48 (34.8)	
Emergency room (n=767)	607 (79.1)	160 (20.9)	
Unadjusted 1-year outcomes, n (%)			
All-cause death	171 (4.5)	29 (2.2)	<0.001
Stroke/systemic embolism	65 (1.7)	8 (0.6)	0.004
Major bleeding	73 (1.9)	9 (0.7)	0.002

Conclusion: These real-world data confirm that suboptimal INR control is associated with an increased risk of severe adverse outcomes. Further analyses for different FIR cut-offs are ongoing.

Abstract P6257 – Table 1. One year bleeding and stroke/SEE rates after treatment in each BMI category

	One Year Major Bleeding Rates (95% Confidence Interval)					One Year Stroke/SEE Rates (95% Confidence Interval)				
	Overall	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	P-value	Overall	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	P-value
BMI Bottom 10% n=1865	4.6% (3.6, 5.6)	4.1% (2.5, 5.6)	4.7% (3.0, 6.4)	5.1% (3.3, 6.7)	0.67	2% (1.3, 2.6)	2% (0.9, 3.1)	1% (0.2, 1.8)	2.9% (1.6, 4.2)	0.02
BMI Middle 80% n=14,435	3.6% (3.3, 3.9	3% (2.5, 3.5)	3.9% (3.4, 4.5)	3.8% (3.3, 4.4)	0.006	1.4% (1.2, 1.6)	1.5% (1.2, 1.9)	1.2% (0.9, 1.5)	1.6% (1.2, 1.9)	0.01
BMI Upper 10% n=1787	3.7% (2.8, 4.6)	3% (1.6, 4.4)	4.4% (2.7, 6.1)	3.7% (2.2, 5.2)	0.55	1.1% (0.6, 1.6)	1.2% (0.3, 2.0)	0.9% (0.1, 1.6)	1.3% (0.4, 2.3)	0.60

Log rank p-values are reported for the comparison of treatments within each BMI subgroup. Due to small numbers, p-values were not significant for all comparison in the extreme bottom or upper 10% BMI values.

P6257 | BEDSIDE
The use of dabigatran according to body mass index: the RE-LY experience

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Introduction: Many pharmaceuticals (not including dabigatran) are dosed according to body weight.
Objective: The purpose of this analysis was to understand efficacy and safety outcomes at 1 year in relationship to body mass index (BMI), and according to treatment assignment in patients with atrial fibrillation (AF).
Methods: In the RE-LY trial, 18,113 patients were randomly assigned to 110 mg or 150 mg dabigatran bid vs warfarin dose adjusted to INR 2.0-3.0. The overall sample median (range) BMI was 27.9 kg/m^2 (10.9 to 76.4). BMI was categorized into three groups based on the bottom 10% ($\leq$22.5 kg/m^2), middle 80% (22.5 to $\leq$36 kg/m^2), and upper 10% ($>$36 kg/m^2). Kaplan-Meier estimated event rates of major bleeding and stroke/SEE (systemic embolization) at 1 year from randomization are reported in BMI groups by treatment. Due to the exploratory nature of the analyses, no p-value adjustment for multiple comparisons was made.
Results: One year bleeding and stroke/SEE rates were higher in patients with the bottom 10% BMI values compared to middle, and upper BMI subgroups (all P-values $<$0.001). Within each BMI subgroups, the 1 year major bleeding rate trends were comparable or lower in those that received 110 mg dabigatran compared to 150 mg dabigatran and warfarin. In contrast, one year stroke/SEE rates were lower in those that received 150 mg dabigatran, compared to the other two treatments in each BMI subgroup (Table).
Conclusion: Patients receiving oral anticoagulation for AF, with a BMI $\leq$22.5 kg/m^2 have an increased risk of major bleeding and stroke/SEE at 1 year, compared to patients with a BMI $>$22.5 kg/m^2. Differences between treatments within each BMI subgroup are consistent with results in the overall trial.

P6258 | BEDSIDE
Usefulness of the SAMe-TT2R2 risk score in identifying patients who will do well with vitamin K antagonist therapy in a community-based cohort of patients with non-valvular atrial fibrillation

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Background: Oral anticoagulant therapy (OAC) is the cornerstone treatment in atrial fibrillation (AF) patients at risk of thromboembolic events. However, time in therapeutic range (TTR) for OAC therapy is critical to prevent the devastating consequences of AF-related thromboembolic complications. There is now a great interest in identifying patients at risk of having a poorer TTR and therefore could be potential candidates for prescribing a new OAC. Recently, a new predictive model, the SAMe-TT2R2 was conceived for this purpose. However, the performance of this risk score in an independent datasets is poorly known.
Aim: To examine the validity of the new SAMe-TT2-R2 score at predicting the quality of anticoagulation, in a sample of outpatients with non-valvular AF.
Methods: Retrospectively, Between June, 2012 and December 2013, all consecutive patients with non-valvular AF on a vitamin-K antagonist who were attending the outpatient Cardiology clinics of a tertiary hospital were recruited. We calculated the SAMe-TT2R2 score in 534 ambulatory patients with non-valvular AF who had $>$12 months of uninterrupted VKA and more than 9 consecutives INR values. The performance of the SAMe-TT2R2 was evaluated by checking its discriminative power (c-index) and calibration ability (Hosmer-Lemeshow goodness-of-fit test) with regard to the 25th, 10th, and 5th percentile as the TTR cut off points.
Results: Mean INR values was 13.9 (SD 1.8); 342 (64%) patients had 15 INR values. The mean TTR (% in Range) was 60% (SD 18). The 25th, 10th, and 5th percentile of the TTR was of 46.7%, 33.3% and 26.7%, respectively. The SAMe-TT2R2 score values ranged from 0 to 5 (201 [39% patients had $\geq$2 points]). The c-index values for the 25th, 10th, and 5th percentiles of the TTR were 0.58 (95%CI 0.52-0.63), 0.65 (95% CI 0.57-0.74), and 0.66 (95%CI 0.58-0.75), respectively. The risk score performed well in terms of calibration as all the p-values of the Hosmer-Lemeshow goodness-of-fit test were $\geq$0.20.
Conclusions: The new SAMe-TTR2 score predicts acceptably poor INR control and could potentially aid decision-making in the management of patients with non-valvular AF.

P6259 | BEDSIDE
The thrombogenic condition in female patients with atrial fibrillation may be caused by left ventricular diastolic dysfunction. Evaluated by propensity score matching

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Background: Female gender is a risk factor for thromboembolism (TE) in atrial fibrillation (AF). But the pathophysiological basis for increased embolic risk in women is not well known, especially in cardiac anatomy and function. The aim of study was to evaluate the cardiac structural and hemodynamic differences between sexes in AF by eliminating well-known clinical risk factors for TE.
Methods: 168 (F/M; 84/84) patients with non-valvular AF were matched by age, presence of diabetes or hypertension and type of AF, using propensity score. The size and function of left ventricle (LV) and left atrium (LA) were measured by echocardiography. Parameters of aortic stiffness (Aortic strain, distensibility and stiffness index) were calculated from ascending aortic diameters in M-mode echocardiography.
Results: The LV mass index and ejection fraction were similar in both groups, but LA volume index was larger in female. Peak mitral E wave velocity, the ratio peak mitral E wave and mitral annular tissue velocity (E/e') were higher and deceleration time was shorter in female than that of male. The presence of SEC tended to be more frequent in female than male (p=0.051). Aortic distensibility was lower and aortic stiffness index was higher in female (Table 1).

Table 1

	Female (N=84)	Male (N=84)	P-value
Left ventricular mass index (g/m^2)	92.3±19.1	94.5±18.9	0.926
Left ventricular ejection fraction (%)	51.9±6.9	54.2±5.8	0.439
Left atrial volume index (ml/m^2)	41.5±14.5	34.4±11.1	<0.001
Peak mitral E wave velocity (m/s)	72.9±17.4	65.1±16.2	0.005
Deceleration time (ms)	162.9±42.3	180.6±41.8	0.007
E/e'	10.7±3.1	9.0±3.6	0.002
The presence of spontaneous echo contrast (n,%)	34 (40.5%)	23 (27.5%)	0.051
Aortic strain (%)	7.33±3.44	8.06±3.22	0.106
Aortic distensibility (cm^{-2} dyn^{-1} 10^{-6})	3.33±1.74	3.95±1.95	0.018
Aortic stiffness index	3.68±2.28	2.98±1.93	0.026

Conclusion: Despite the similar clinical settings, LV diastolic function was worse in female than male with AF. The worse diastolic LV function may induce LA stasis and this may contribute greater risk of LA thrombus formation in female. LV diastolic dysfunction could be explained by the higher aortic stiffness in female than male.

P6260 | BEDSIDE
Risk stratification in AF: thrombo-embolic risk and or INR variability?

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AF carries twice the mortality when compared to those without diagnosed AF. Several variables are associated with a poor outcome; the CHA2DS2VASc score is an extremely useful tool to predict thrombo-embolic complications. On the other hand; the INR variability is a treatment efficacy variable also associated with morbidity and mortality in patients receiving warfarin. Our aim was to compare the prognostic value of the CHA2DS2VASc versus the INR variability or its combination to predict mortality.
Methods: We studied 589 patients from our AF-Cohort, all receiving warfarin, with more than 6 INRs (mean 15) performed in the last two years. The CHA2DS2VASc and the INR variability were estimated using TTR, % of INRs within range, SD of the INRs, 95%CI of the INRs. Survival curves with the KM method (log Rank test) were performed. Proper cut-off points were determined by ROC curves The population was divided into two groups; CHA2DS2VASc $>$1 and CHA2DS2VASc of 0 or 1. The same calculations were performed with the INR variability with the different indexes and cut-off points.
Results: 65/589 died during the study period (11%), the most frequent causes of dead were bleeding, ischemic stroke, and heart failure. 128 pts had a CHA2DS2VASc $<$2, and 461 equal or above 2, mortality was 7% versus 12% respectively, survival curves were significantly different (p=0.001). When we compared the SD of the INRs with a cut-off point of 0.8, mortality was 6% versus 19% respectively (p=0.0001). When we combined the CHA2DS2VASc $<$2 and SD of the INRs below 0.8 versus a CHA2DS2VASc above 2 and a SD of the INRs above or equal to 0.8; mortality was 8% versus 31%, respectively (p=0.00001).
Conclusions: Assessment of both CHA2DS2VASc and INR variability appears to be extremely useful to predict mortality in patients with AF receiving warfarin.

The SD of the INRs above or equal 0.8 emerges as a strong mortality predictor compared to other INR variability indexes.

P6261 | BEDSIDE
Analysis of antithrombotic therapy prescription for the prevention of stroke and systemic embolism in patients with atrial fibrillation in clinical practice

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Antithrombotic therapy (ATT) prescription in patients with atrial fibrillation (AF) is the only medical intervention affecting the prognosis. CHA2DS2-VASc score is recommended for stroke risk stratification in all patients with AF. The latest review of practice guidelines extended the number of indications for anticoagulant therapy, especially for novel anticoagulants (NOAC) prescription.
Purpose: The purpose of this study was to analyze physician's tactics in ATT prescription for cardiogenic embolism prevention in patents with AF.
Materials: This study involved an anonymous survey conducted among 382 physicians (160 cardiologists and 262 internists). The first question was: "In what number of cases do you use CHA2DS2-VASc score to stroke risk stratification in patients with AF?" The second question asked: "Which antithrombotic drugs do you recommend for cardiogenic embolism prevention in patient with AF?"
Results: The received data showed that 113 physicians (50%) didn't use CHA2DS2-VASc score, 78 physicians (20%) used it less than in 50% of cases, 111 specialists (29%) – more, than in 50% of cases and 80 (21%) respondents evaluated stroke risk in all patents with AF. The mostly prescribed drug for cardiogenic embolism prevention was warfarin (30%), second and third place took acetylsalicylic acid (19%) and clopidogrel (16%) in monotherapy. Dabigatran and rivaroxaban recommended 10% and 8% of physicians respectively. 8% of respondents preferred acetylsalicylic acid and clopidogrel combination, and a small number of physicians recommended other drugs, such as feniline (4%), syncumar (1%), dipyridamole (2%), pentoxifylline (2%).
Conclusions: According to results of our study, only 1 of 5 physicians always used CHA2DS2-VASc score for stroke risk stratification in patients with AF. One third of them recommended warfarin, every fourth prescribed drugs which safety and efficacy for stroke prevention in patients with AF hadn't been validated in large studies, and only 18% of specialists preferred NOAC as it recommended in actual clinical practice guidelines.

EMBOLIC RISKS IN ATRIAL FIBRILLATION

P6263 | BEDSIDE
Silent cerebral infarcts and its association with clinical and echocardiographic factors in patients with non valvular atrial fibrillation

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Purpose: In addition to overt stroke atrial fibrillation (AF), may also cause "silent" cerebral ischemic areas with some neuropathological consequences. The aims of the study were to evaluate prevalence of large (≥15mm) silent cerebral infarcts (SCI) and its association with clinical and echocardiographic factors in patients with AF.
Methods: We examined 134 patients with non valvular AF. Among them 15,67% (n=21) of patients had paroxysmal AF, while others 84,33% (n=113) persistent and long lasting persistent AF. The mean age was 60,6 y.o., mean left ventricle ejection fraction (LVEF) 55,34%, mean left atrial appendage velocity (LAAV) 35,63 cm/s, mean anamnesis of atrial fibrillation 3,72 years, mean duration of arrhythmia episode 6,78 month, mean CHA2DS2VASc score 2,23, mean International Normalized Ratio (INR) was 1,5. 70,15% (n=94) of patients were males and 29,85% (n=40) were females. 23,13% (n=31) had diabetes. Arterial hypertension was found in 82,09% (n=110) of patients. There were no cases of prior stroke among patients. All patients underwent to anamnesis, neurological, biochemical examinations, transoesophageal (in a case of persistent form), transthoracic echocardiography and multispiral computed tomography of the brain. Severe carotid stenosis was excluded by carotid duplex scanning. According to current recommendations SCI was defined as imaging ≥3mm or neuropathological evidence of central nervous system infarction, without a history of acute neurological dysfunction attributable to the lesion.
Results: SCI were detected in 33,58% (n=45) of patients, and in total infarcts ≥15mm were detected in 11,19% (n=15) of patients. SCI≥15mm were found in 19,05% of patients with paroxysmal AF and in 9,73% of patients with persistent AF, p=0,2. By neurological examination all patients with SCI≥15mm had some evidences of chronic neurological deficit. SCI≥15mm were significantly associated with CHA2DS2VASc score≥2 OR=8,82 (95%CI 6,8-10,9), p=0,014; LAAV<30 cm/s OR=4,89 (95%CI 3,6-6,2), p=0,012; creatinine clearance (CCl)<90 ml/min OR=4,85 (95%CI 3,3-6,4), p=0,03; complex plaque in aorta ≥5 mm OR=3,34 (95%CI 2,2-4,5), p=0,035; LV wall motion abnormalities OR=2,94 (95%CI 1,9-4,0), p=0,045; and was not associated with severe SEC 4+ and low LVEF<45%, p>0,05. In the multivariate logistic model, LAAV<30 cm/s, p=0,017 and CCl<90 ml/min, p=0,035 were independently associated with SCI ≥15mm.
Conclusions: Large SCI ≥15mm were not rare findings in patients with AF. Left atrial appendage dysfunction and chronic renal impairment were independently associated with these lesions.

P6264 | BEDSIDE
Is oral anticoagulation needed in patients with atrial fibrillation, stent implantation and low-moderate risk of stroke?

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Thromboprophylaxis for patients with coronary artery disease and atrial fibrillation (AF) may often be antiplatelet therapy when there is a low or moderate risk of stroke (CHADS2 score=0 or 1), particularly when patients experience an acute coronary syndrome or undergo intracoronary stent placement. Some physicians may be reluctant to prescribe oral anticoagulation (OAC) in these patients and several recent guidelines propose slightly different management in such settings. Our goal was to evaluate whether treatment with an OAC is appreciably beneficial in these AF patients.
Methods: All patients with AF and stent implantation seen between 2000 and 2010 in 3 academic hospitals were identified in a database and followed up for mortality, stroke and bleeding events. The CHADS2 score was calculated for each patient as initially described, based on 2 points for a history of stroke or TIA, and 1 point each for age ≥75, hypertension, diabetes, and cardiac failure.
Results: Among all patients seen between 2000-2010, 343 had AF, coronary stent placement and CHADS2 score=0 or 1. In these patients, OAC was prescribed on an individual basis for 144 patients (42%) and no OAC in the remaining 199 patients (58%). During a 1-year follow-up, 17 strokes/thromboembolic events (5.0%), 29 major bleedings (8.5%) and 30 deaths (8.7%) were recorded. Patients under OAC had a non significant lower risk of stroke than those not treated with OAC (2.8% vs 6.5%, p=0.14), a non significant higher risk of bleeding (11.8% vs 6.0%, p=0.08) and a lower all-cause mortality (4.9% vs 11.6%, p=0.03).
Conclusions: In one of the largest series of AF patients with coronary stent implantation and a CHADS2 score =0-1, prescription of oral anticoagulation was associated with a trend towards lower risk of stroke and higher risk of bleeding, and with a significantly lower mortality.

P6265 | BEDSIDE
Use of novel oral anticoagulants in patients undergoing atrial fibrillation catheter ablation

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Background: Novel oral anticoagulants (NOACs) for stroke prevention in atrial fibrillation (AF) are increasingly used in the general AF population, but experience in patients undergoing AF catheter ablation is limited. Here, we report practice patterns and short-term outcomes of different anticoagulation strategies before and after AF ablation.
Methods: Pre- and postablation oral anticoagulation was assessed in 893 consecutive patients (63% male, age 62±10 years). Intravenous heparin use and activated clotting time were monitored during ablation. 30-day bleeding and thromboembolic complication rates were assessed.
Results: Patients presented with Vitamin-K-antagonists (VKA), NOACs or antiplatelets/no anticoagulation in 45%, 39% and 16%, respectively. Among the patients on NOACs, dabigatran, rivaroxaban and apixaban was used in 41%, 56% and 3%, respectively. Among patients with VKA, INR was 2 – 3 in 80%, while NOACs were discontinued 24 hours before the procedure. Using 14146±4540 units of heparin, ACT >300 sec was achieved in 63% of the total population. ACT >300 sec was more frequently achieved with VKA (81%) compared with dabigatran (64%), apixaban (67%) or rivaroxaban (53%), although patients treated with NOACs required more heparin (14703 in dabigatran, 15838 in rivaroxaban, 16750 in apixaban vs. 12303 in VKA). While there was only one thromboembolic complication, there were 1,6% bleeding complications (0,9% pericardial tamponade, 0,7% groin); Bleeding rates were 0,6% with dabigatran, 1,4% with rivaroxaban, 1,5% with VKA, 3,2% with low-molecular weight heparin and 3,1% with no prior anticoagulation. NOACs were initated within 12 - 18 hours after ablation and included dabigatran, rivaroxaban and apixaban in 25%, 30% and 2%, respectively, while 43% remained on VKA.
Conclusions: There is substantial use of NOACs before and after AF catheter ablation. While bleeding and thromboembolic complications are rare with different regimens, heparin use and ACT are substance-dependent. Further studies are needed to better define the role and specific management of NOACs in the setting of AF catheter ablation.

P6266 | BEDSIDE

Trends in antithrombotic management of atrial fibrillation after the last update of ESC guidelines: follow-up data from the PREFER in AF registry

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Purpose: The 2012 focused update of the ESC guidelines for the management of atrial fibrillation (AF) recommended the use of anticoagulant therapy for the prevention of thromboembolic events for all patients with AF except in those at low risk. However, implementation tends to be incomplete or only applied to a subset of patients. We evaluated the impact of these recommendations in clinical practice of different European countries

Methods: The PREvention oF thromboembolic events – European Registry in Atrial Fibrillation (PREFER in AF) recruited unselected patients diagnosed of AF in Austria, France, Germany, Italy, Spain, Switzerland and the United Kingdom from Jan 2012 to Jan 2013. We report the data collected at enrolment into the study and follow-up performed 1 year later.

Results: 7243 patients were enrolled from 461 sites. The mean age was 71.5±11 years, 60.1% were male and the mean CHA2DS2-VASc score was 3.4±1.8. Anticoagulation rate reached 85.6% of those with CHA2DS2-VASc score ≥2 (4793 of 5600), and 70.1% of those with CHA2DS2-VASc score of 1 (468 of 668) at the baseline visit. The overall anticoagulation rate at follow up was slightly lower as compared with baseline (from 82.3 to 80.0%). There was a significant reduction in the use of vitamin K antagonists (VKA) alone (from 66.3 to 61.8%). In parallel, the use of novel oral anticoagulants (NOACs) raised from 6.1 to 12.6%, mainly due to a marked increase of oral factor Xa inhibitors [rivaroxaban, apixaban] (from 1.9 to 6.0%), and in lesser amount due to oral thrombin inhibitors [dabigatran] (from 4.0 to 6.5%). Substantial inter-country differences were noted with higher uptake of NOACs in Germany, France and Spain. Most of the combination treatments judged inappropriate according to the last ESC guidelines were progressively discontinued, such as the combined long-term use of VKA and antiplatelet (AP) agents (from 9.9 to 5.7%), and the use of APs agents as monotherapy (from 11.2 to 8.0%).

Conclusions: The antithrombotic management of AF patients in 2013 in Europe has been substantially adapted to guideline recommendations, and oral anticoagulants are administered to a majority of eligible patients. However, implementation is not complete and there are still prescription patterns that should be adequately targeted.

P6267 | BEDSIDE

Anticoagulation treatment safety with vitamin K antagonists and novel oral anticoagulants within the registry of patients with non-valvular atrial fibrillation

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Background: Thromboembolic events (TEE) in patients with atrial fibrillation (AF) are associated with increased cardiovascular mortality by means of cardioembolic stroke. However, in Russia very small amount of patients are taking anticoagulants. By the way, now cardiologists may also prescribe novel oral anticoagulants (NOAC) with no need of routine laboratory monitoring and dose changing but routine clinical experience with NOAC is still limited.

Aim of the study: For detalization of actual state of art in routine clinical practice of anticoagulant treatment registry (RAFAC – Registry of patients with Atrial Fibrillation with and without AntiCoagulants) of patients with non-valvular AF was organized on the basis of anticoagulant clinic.

Subjects: Up to date 681 patients with non-valvular AF are included in the RAFAC registry; 70,2% are women (mean age – 70,4 years) and 29,8% - are men (mean age – 63,2 years). 667 patients (98%) had at least 1 point according to CHA2DS2-VASc score. Among those only 423 (63,4%) were taking anticoagulants: 309 patients (73,0%) were taking warfarin and 114 patients – NOAC (27,0%; 22,4% from all anticoagulated patients took dabigatran and 4,6% - rivaroxaban).

Results: Within 1 year no TEE were registered in all the patients in the Registry. Minor bleedings were seen in 6,5% of anticoagulated women and 9,5% of anticoagulated men, major bleedings were not registered. Only few (21%) patients on warfarin had time within the therapeutic range (TTR) more than 60% as it should be. Bleedings occurred significantly higher in patients on warfarin (8,4%) in comparison with patients on NOAC (4,3%; $p<0,05$). As expected, mostly frequent bleedings occurred in patients with 6 points according to CHA2DS2-VASc (12,7% of patients with bleedings). However, patients with only 1 point according to CHA2DS2-VASc had also rather high bleeding rate (8,5%) that should be discussed in terms of necessity of anticoagulation in these patients with low-intermediate risk of TEE.

Conclusions: Registry RAFAC data confirm significant underuse of oral anticoagulants for thromboembolism prevention in patients with non-valvular AF even in routine medical care of large cardiovascular centers. Less than quarter of patients on warfarin are in >60% of TTR that may partly explain higher bleeding rates in patients of vitamin K antagonists and in future may also leads to low efficacy of such treatment. NOAC (dabigatran and rivaroxaban; apixaban has been registered in Russia only in the end of 2013) confirm their safety in routine practice in this group of patients.

P6268 | BEDSIDE

Comparison of atrial fibrillation patients with and without an initial awareness of rhythm disturbance in the PREFER in AF registry for outcomes and management differences

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Background: Patients with atrial fibrillation (AF) may present initially with or without the awareness of an irregular rhythm. Contemporary outcome data comparing these patients and management strategies are unavailable.

Methods: Between Jan 2012 and Jan 2013, the PREFER in AF registry enrolled consecutive patients with AF from 461 centres in Austria, France, Germany, Italy, Spain, Switzerland and UK. Patients were divided into those with symptoms (S) and those who were asymptomatic (AS) using the respective European Heart Rhythm Association score of 2-4 (S) and 1 (AS).

Results: Of the 7,243 patients enrolled with baseline data, 40% were female, mean age 72 years. Overall 30% had paroxysmal, 24% persistent, 7% long standing persistent and 39% had permanent AF. Percentages were 22%, 26%, 7% and 45% in the asymptomatic patients, respectively. CHA2DS2VASc scores on average were 3.4 for S and 2.9 for AS patients.

To date, at follow-up of 6412 patients with 1 year data, additional strokes had occurred in 0.9% (54/5695) of S and 1.6% (8/501) of AS patients with respective TIA rates of 0.6% (37/5695) and 1.2% (6/501).

Re: medications, 11% of S and 9% of AS were not on anti-platelet or anti-thrombotic medications, with 13% in both groups on a novel oral anticoagulant (NOAC) at the follow-up visit (Table 1).

Table 1. Medication intake at Baseline and Follow-up

	Patients with symptoms (S) N=5695		Asymptomatic patients (AS) N=501	
	n	%	n	%
Baseline Visit				
No anti-platelet or anti-thrombotic medication	337	5.9	29	5.8
NOAC	357	6.3	26	5.2
Follow-up Visit				
No anti-platelet or anti-thrombotic medication	540	11.2	38	8.8
NOAC	628	13.0	58	13.4

Conclusions: Our data show that in a large registry of contemporary management of AF, stroke and TIA outcomes are similar for patients with and without symptomatic awareness of AF over 1 year follow-up. Similar low proportions of patients are started on novel oral anti-coagulants (NOAC), but more patients are not taking either anti-platelet or anti-thrombotic therapy, which is a cause for concern.

P6269 | BEDSIDE

Functional remodeling rather than morphological character of left atrium is a powerful predictor for the occurrence of stroke in patients with atrial fibrillation

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Introduction: Optimal identification of the high risk patients for stroke is a crucial issue in management of atrial fibrillation (AF). In addition to the clinical risk stratification schemes, multi-detector computed tomography (MDCT) can also confer useful information to select the vulnerable patients for stroke.

Methods: We studies 118 patients (80 male). Group I included 21 controls, group II included 68 patients with AF and no history of stroke, group III included 29 patients with AF related stroke. A 64-slice CT was performed to evaluate the anatomic and functional characteristics of left atrium (LA) and appendage (LAA). The pouch of LA and four types of LAA morphologies (Cactus, Chicken Wing, Windsock and cauliflower) were depicted. In addition, the active transport function [(volume at P wave beginning -minimal volume)/volume at P wave begin-

ning] and passive transport function [(maximal volume- volume at P wave beginning)/maximal volume] of LA and LAA were assessed by dynamic CT.
Results: The gender, body mass index were similar among three groups. However, the age was elder and CHADS2 score was higher in group III. The incidence of LA pouch was similar among the three groups (33% vs 29% vs 28%, p=0.90). The distribution of different LAA morphologies were also similar among the three groups (p=0.11). On the other hand, the active transport function of LA and LAA (LA: 0.31±0.06 vs 0.23±0.14 vs 0.11±0.10; LAA: 0.48±0.17 vs 0.34±0.21 vs 0.13±0.19, both p<0.001) were significantly reduced in patients with AF and stroke. But the passive transport function of LA and LAA were similar among the three groups (P=0.14 for LA, p=0.43 for LAA)
Conclusion: LA pouch is not an uncommon finding and it is not associated with the stroke in patients of AF. The categories of LAA morphologies among the three patient groups are not significantly different. our findings showed that the impaired active transport function of LA and LAA correlated significantly with the occurrence of stroke in patients with AF.

P6270 | BEDSIDE
Prevalence of left atrial appendage thrombus according to CHADS2 score level in patients with atrial fibrillation

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Transesophageal echocardiography (TEE) is performed routinely in patients with AF of >48h in order to exclude left atrial appendage thrombus (LAA-T) prior to cardioversion. The purpose of this study was to assess the prevalence of LAA-T according to the CHADS2 score.
Methods: We analyzed all TEEs performed for patients with AF of >48h, prior to cardioversion. Patients with significant valvular disease, prosthetic valve, or hypertrophic cardiomyopathy were excluded.
Results: A total of 1504 TEEs were reviewed. The mean age was 73.6±11.3 years, 708 (47%) females, and mean CHADS2 score was 2.3±1.2. (median [interquartile range] was 2 [1–3]). LAA-T was detected in 165 (11%). Figure 1 summarizes the % of patients with LAA-T at each CHADS2 score level. Multivariate logistic regression with all components of CHADS2 score as covariates revealed 3 independents risk factors for LAA-T: prior stroke (OR 2.32 95%CI[1.52-3.58]; p<0.0001), CHF (OR 1.70 95%CI [1.22–2.38]; p=0.002), and DM (OR 1.55 95%CI [1.10–2.20]; p=0.012).

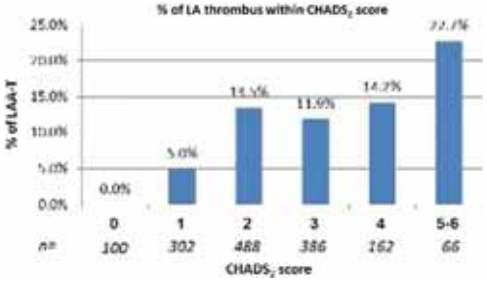

Figure 1. CHADS2 LAA.

Conclusion: The odds of finding an LAA-T in patients with AF >48h increased with the CHADS2 score level. No LAA-T was detected in patients with AF and CHADS2 score of 0. It might be reasonable to omit TEE as a screening examination prior to cardioversion in AF patients with CHADS2 score of 0, but patients with score ≥1 require TEE in order to exclude LAA-T prior to cardioversion.

P6271 | BEDSIDE
CHA2DS2-VASc vs. CHADS2 at predicting the risk of stroke and death in a community-based cohort of patients with non-valvular atrial fibrillation who are on anticoagulation

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Background: CHA2DS2-VASc risk score was seen to be more reliable than the CHADS2 score for identifying patients with non valvular atrial fibrillation (AF) who are at risk of stroke. The predictive superiority of the CHA2DS2-VASc over the CHADS2 in anticoagulated patients with non valvular AF is not well known.
Aim: To assess the predictive ability of CHA2DS2-VASc and CHADS2 in predicting the composite endpoint of stroke and death in non valvular AF patients on vitamin K antagonist.
Methods: Retrospectively, from June/2012 to December/2013, 534 patients with non-valvular AF on vitamin-K antagonist who were attending the outpatient Cardiology clinics of a tertiary hospital in Spain were recruited. We calculated CHA2DS2-VASc and CHADS2 from the variables they include. The Cox regression analyses were used to assess the association (in terms of hazard ratio *HR*) between each of the two risk schemes and the study endpoint. Data regarding stroke and death was collected at 10 (SD=3) months. The performance of both risk scores was computed by using area under the ROC (receiver operating characteristics) curves [AURc].
Results: Mean age was 74 (SD 11) years, and 216 (40.4%) were women. CHADS ranged from 0 to 6 points, while CHADS-VASc ranged form 0 to 8 points. According to CHADS scheme there were 8.8% at low risk (0 points), 20% at intermediate risk (1 point), and 71.2% at high risk (≥2 points) of non fatal stroke and death at 10 (SD 3) months. However, according to CHA2DS2-VASc, 5.4%, 5.6%, and 89% of patients were classified as having low, intermediate and high risk, respectively. At 10 (SD 3) months, 14 events were recorded: 5 patients suffered a non fatal stroke and 9 patients died. 13 out of the 14 events were found in the high risk category of the CHA2DS2-VASc (one event in the intermediate risk category). In contrast, using the CHADS2 classification system, 11 of 14 events occurred in the high risk strata, 2 of 14 in the intermediate risk strata, and 1 of 14 in the low-risk category. HR for the association between the CHA2DS2-VASc (as a continuous category) and stroke/death during follow-up was 1.4 (95%CI 1.007-2.041; p=0.046), similar to the HR obtained by using the CHADS2 score (HR 1.4 [95%CI: 1.001-2.248]; p=0.049). CHA2DS2-VASc exhibited a better predictability than did CHADS2 as was seen by the AURc: 0.67 [95%CI 0.52 to 0.80; p=0.03] vs. 0.63 [0.46 to 0.79; p=0.11].
Conclusion: In our study the rate of stroke in patients with non valvular AF was nearly 1% despite anticoagulation. CHA2DS2-VASc outperformed the old CHADS2 in predicting the risk of stroke and death in these patients

ANTICOAGULANTS AND ATRIAL FIBRILLATION

P6273 | BEDSIDE
Polypharmacy and bleeding in atrial fibrillation: a real-world prospective cohort study on patients using vitamin-K antagonists

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Purpose: Polypharmacy is associated with adverse clinical outcome and frailty. In view of this, physicians are often reluctant to prescribe vitamin-K antagonists (VKA) in patients with polypharmacy due to the fear of bleeding complications. However, it has never been thoroughly investigated whether polypharmacy is associated with bleeding in patients using VKA for stroke prevention in atrial fibrillation (AF).
Methods: Patients with AF using VKA were contacted in May 2011 with questions regarding their medical history. During follow-up bleeding events were monitored. Clinically relevant bleeding comprised all bleedings of critical organs or leading to death, contact for medical aid, or dose adjustment of the VKA. Follow-up ended in August 2012. Patients were categorized in groups according to the number of concomitant drugs.
Results: In total 2390 patients with medication data were included. The median age was 77 years (IQR 69-82) and the median CHA2DS2-VASc score was 4 (IQR 3-5). Patients with more drugs were older and comorbidities were more often present. During a mean follow-up of 1.2 years, overall 17% of the patients suffered from one or more bleeding events. When comparing the three groups, the proportion of patients with one or more bleeding events increased with the number of drugs taken concomitantly (Table 1). After correction for age and gender, the number of concomitant drugs remained significantly associated with all bleeding.

Table 1

	Number of patients with a bleeding event categorized by the number of drugs			P-value
	1–4 (N=641)	5–7 (N=989)	≥8 (N=760)	
Patients with:				
Minor bleeding	63 (9.8%)	116 (11.7%)	101 (13.3%)	0.13
Clinically relevant bleeding	34 (5.3%)	66 (6.7%)	59 (7.8%)	0.18
All bleeding	91 (14.2%)	161 (16.3%)	150 (19.7%)	0.018

Conclusions: In this real-world cohort of AF patients using VKA, polypharmacy is associated with more bleeding events during follow-up. Moreover, polypharmacy was associated with older age and the presence of more comorbidities. Perhaps the NOACs, with their better safety profile, could be an attractive alternative in these patients.

Abstract P6274 – Table 1

	Pace-maker or ICD	Annual rate dabigatran 110 mg bid	Annual rate dabigatran 150 mg bid	Annual rate warfarin	DE 110 mg vs. warfarin HR (95% CI)	DE 150 mg vs. warfarin HR (95% CI)
Outcome (ITT)						
Stroke + systemic embolism	Yes/No	1.47/1.55	1.18/1.10	2.20/1.65	0.67 (0.38, 1.17)/0.94 (0.76, 1.17) p-inter = 0.26	0.54 (0.30, 0.96)/0.67 (0.53, 0.85) p-inter = 0.48
Death	Yes/No	3.83/3.74	3.87/3.61	4.54/4.07	0.83 (0.57, 1.19)/0.92 (0.80, 1.05) p-inter = 0.65	0.84 (0.59, 1.20)/0.88 (0.77, 1.02) p-inter = 0.82
Vascular death	Yes/No	2.87/2.37	2.43/2.26	3.55/2.57	0.80 (0.53, 1.21)/0.92 (0.78, 1.10) p-inter = 0.56	0.68 (0.44, 1.04)/0.88 (0.74, 1.04) p-inter = 0.28
MI (including silent)	Yes/No	1.10/0.79	0.92/0.79	0.99/0.59	1.12 (0.54, 2.32)/1.34 (0.96, 1.86) p-inter = 0.64	0.92 (0.44, 1.94)/1.34 (0.97, 1.87) p-inter = 0.36
Stroke/SEE, MI (incl. silent) or vascular death	Yes/No	4.71/4.11	3.67/3.56	5.68/4.10	0.82 (0.59, 1.14)/1.00 (0.88, 1.15) p-inter = 0.27	0.64 (0.45, 0.90)/0.87 (0.75, 1.00) p-inter = 0.10
Outcome (Safety set)						
Major bleed	Yes/No	4.76/2.65	3.49/3.40	4.24/3.45	1.12 (0.77, 1.64)/0.76 (0.64, 0.90) p-inter = 0.06	0.82 (0.55, 1.22)/0.98 (0.84, 1.15) p-inter = 0.40
Life-threatening bleed	Yes/No	1.76/1.08	1.43/1.34	1.73/1.76	1.02 (0.56, 1.87)/0.61 (0.47, 0.78) p-inter = 0.12	0.82 (0.44, 1.53)/0.76 (0.60, 0.96) p-inter = 0.83
ICH	Yes/No	0.18/0.19	0.40/0.22	0.55/0.80	0.32 (0.07, 1.56)/0.23 (0.14, 0.39) p-inter = 0.71	0.72 (0.23, 2.28)/0.28 (0.17, 0.45) p-inter = 0.14

P6274 | BEDSIDE
Dabigatran versus warfarin in patients with pacemaker or defibrillator wires in the RE-LY trial: the role of contact activation

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Background: Contact activation of coagulation may occur when blood is exposed to artificial surfaces, such as electrodes from pacemaker (PM) or implantable cardioverter-defibrillators (ICDs).
Aim: To evaluate the efficacy and safety of dabigatran (D) compared to warfarin in patients with and without electrode wires from pacemakers or ICDs.
Methods and results: Of the 18,113 patients in RE-LY, 2,124 patients (11.7%) had a PM (10.7%) or ICD (1%), with 1.2% having both. Patients with PM or ICD were older (73.4 vs. 71.2 years, $p<0.001$), had more congestive heart failure (40.5% vs. 30.8%, $p<0.001$), coronary artery disease (40.6% vs. 26.1%, $p<0.001$), previous myocardial infarction (25.3% vs. 15.4%, $p<0.001$), higher CHADS2 scores (2.3 vs. 2.1 $p<0.001$), moderate renal impairment with CrCL of 30 to 50 mL/min (26.3% vs. 18.2%, $p<0.001$), and were vitamin K antagonist-experienced (62.3% vs. 47.9%, $p<0.001$). The effect of D vs warfarin was similar for all efficacy and safety end points in patients with or without devices (p-value for interaction NS).
Conclusions: Atrial fibrillation patients with PM and/or ICD disease were more likely to have concomitant cardiovascular diseases. The relative benefit of Dabigatran over warfarin in the population with PM or ICD was maintained. There was no evidence of excessive coagulation activation.

P6275 | BEDSIDE
Risk of gastrointestinal adverse effects of dabigatran etexilat compared with warfarin among patients with atrial fibrillation

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Background: Dabigatran reduces the tromboembolic risk in patients with atrial fibrillation but as an adverse effect dabigatran use has been linked to gastrointestinal bleeding and adverse reactions. The extent of real-world dabigatran-related gastrointestinal adverse reactions is unknown. We examined the risk of gastrointestinal adverse reactions (use of proton pump inhibitors [PPI]) of dabigatran etexilat compared with warfarin used for tromboprophylaxis among patients with atrial fibrillation.
Methods: We assessed information from Danish nationwide registries and obtained individual-level information on hospital admissions, prescription claims, and time of death. The outcome was initiating treatment with PPI analyzed using Cox regression models adjusted for CHA2DS2-VASc score, HAS-BLED score, and treatment with PPI 180 days before initiating warfarin or dabigatran. As referent in the models we used warfarin initiators.
Results: From 1 August 2011 until 31 December 2012 we identified six groups: warfarin initiators (n=3357); dabigatran initiators all (n=3837), dabigatran initiators 150 mg twice daily (n=2139); dabigatran initiators 110 mg twice daily (n=1698); shifters from dabigatran to warfarin (n=59); and shifters from warfarin to dabigatran (n=2362). The use of PPIs was not significantly different between warfarin initiators and dabigatran initiators all (hazard ratio [HR]: 0.99, 95% confidence interval [CI]: 0.84 to 1.16). In addition, there was no significant difference between warfarin initiators and dabigatran initiators 150 mg (HR: 0.84, 95% CI: 0.7 to 1.01), or dabigatran initiators 110 mg (HR: 1.14, 95% CI: 0.96 to 1.35). Contrary, we found that shifters from warfarin to dabigatran were in a significantly higher risk of initiating PPI (HR: 1.80, 95% CI: 1.54 to 2.10). The shifters from dabigatran to warfarin were a small group compared with the warfarin initiators and the difference between the two groups was not statistically significant (HR: 1.37, 95% CI: 0.75 to 2.51).
Conclusions: In patients with atrial fibrillation, initiating treatment with dabigatran was not associated with higher frequency of subsequent PPI use, as compared with warfarin. However, among those who shifted from warfarin to dabigatran; PPI use was more frequent than those initiated on warfarin. The results indicate that dabigatran is not associated with a higher risk of gastrointestinal adverse reactions, compared with warfarin, while shifters from warfarin to dabigatran, may have higher propensity for gastrointestinal adverse reactions.

P6276 | BEDSIDE
Atrial fibrillation and anticoagulation underuse in patients with permanent pacemakers- risk factors for cognitive impairment?

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Introduction: Atrial fibrillation (AF), in addition to macroembolic complications, may also produce multiple cerebral ischemic areas due to microembolic phenomena and transient hypoperfusion, eventually leading to a progressive cognitive impairment and even to acclaimed vascular dementia.
Aims: To determine whether atrial fibrillation (AF) in stroke-free patients with cardiac pacing is associated with impaired cognition and structural abnormalities of the brain and to determine the proportion of these patients who were receiving anticoagulation to prevent thromboembolic stroke.
Methods: 108 patients with non-valvular atrial fibrillation (NVAF) with permanent pacemaker and no history of stroke, and transient ischemic attacks were consecutively examined. All cases underwent physical and paraclinical examination. To investigate the cognitive status, subjects underwent the neuro-psychological rating scale Mini Mental State Examination (MMSE). Patients with cognitive disturbances underwent cerebral CT and TEE.
Results: The 108 patients with AF and ECS (mean age 68.1±0.65 years; 54% M) were evaluate. Forty five patients (42%) diagnosed with AF had no prior documented diagnosis of AF, and the majority had no symptoms suggesting AF. According to CHA2DS2-VASc score 73,1% of patients were in high tromboembolic risk (group I), 22,3% in moderate risk (group II) and 4,6% in low risk (group III). Cognitive status as assessed by MMSE was significantly different in the 3 groups: group 1 - 24.9±2.9; group 2 - 25.9±2.9; and group 3- 28.1±1.9 ($P<0.01$). Brain CT has shown lacunar or ischemic changes in 52% of patients with cognitive disturbances. About 75% of them have had indices for thrombus formation or spontaneous contrast in the left auricle. In the group with cognitive impairment predominated elder subjects (>65 years)- 73%, with III-IV NYHA heart failure, with ejection fraction <40% (63%), with arterial hypertension grade III (88%) and diabetes mellitus - 33%. The anticoagulation rate in these patients was 18%, and only 8% on an optimal treatment level (INR 2.0-3.0).
Conclusion: Atrial fibrillation is a factor which correlate with low cognitive function in patients with pacemakers. The results obtained support the use of anticoagulant therapy whenever indicated. This might prevent not only major cerebrovascular accidents, but also the less obvious clinical outcome of cognitive function loss.

P6277 | BEDSIDE
Interleukin-6 and C-reactive protein and risk for cardiovascular events and death in anticoagulated patients with atrial fibrillation

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Purpose: Atrial fibrillation (AF) is associated with inflammatory activity. The association of inflammatory biomarkers with outcomes in AF needs further elucidation.
Methods: In the ARISTOTLE trial 18,201 patients with AF and at least one addi-

Abstract P6277 – Table 1. Outcomes according to IL-6 and CRP

Outcome	IL-6 (quartiles in rows)			CRP (quartiles in rows)		
	Events (%/yr)	HR (Q group 1 as reference) (95% CI)	p-value effect of biomarker level	Events (%/yr)	HR (Q group 1 as reference) (95% CI)	p-value effect of biomarker level
Stroke or systemic embolism	85 (1.08)		0.1754	98 (1.34)		0.8383
	88 (1.30)	1.11 (0.82–1.50)		97 (1.37)	1.02 (0.77–1.36)	
	121 (1.71)	1.37 (1.02–1.83)		94 (1.34)	1.03 (0.76–1.38)	
	102 (1.53)	1.16 (0.83–1.60)		108 (1.59)	1.14 (0.84–1.55)	
Death	137 (1.70)		<0.0001	198 (2.65)		<0.0001
	191 (2.77)	1.37 (1.09–1.71)		234 (3.22)	1.23 (1.01–1.49)	
	278 (3.82)	1.67 (1.35–2.06)		246 (3.43)	1.24 (1.02–1.50)	
	469 (6.86)	2.32 (1.88–2.86)		390 (5.59)	1.63 (1.35–1.97)	
Major bleed	138 (1.89)		0.0071	171 (2.53)		0.4194
	148 (2.39)	1.10 (0.87–1.40)		169 (2.61)	1.04 (0.84–1.29)	
	172 (2.66)	1.14 (0.90–1.44)		148 (2.31)	0.91 (0.72–1.14)	
	216 (3.69)	1.48 (1.16–1.89)		183 (3.04)	1.09 (0.87–1.37)	

tional risk factor for stroke were randomized to apixaban or warfarin and followed for a median of 1.8 years. Plasma concentrations of IL-6 and CRP, were analyzed in samples obtained at randomization. Association between quartile groups of IL-6 and CRP and clinical outcomes were analyzed by Cox regression adjusted for known cardiovascular risk factors and other cardiac biomarkers.
Results: The IL-6 median level was 2.3 ng/L with interquartile range 1.5-3.9 ng/L. The CRP median level was 2.2 mg/L with interquartile range 1.0-4.8 mg/L. The relations between the IL-6 and CRP quartiles and outcomes are shown in the table. There was no interaction between inflammation marker levels and the effects of apixaban versus warfarin on outcome events.
Conclusions: In anticoagulated patients with AF, inflammatory activation markers are not associated with increased risk of stroke, despite the significant association with mortality. The IL-6 level is also related to the risk of bleeding.

P6278 | BEDSIDE
Novel oral anticoagulants vs. warfarin with heparin bridging peri-ablation of atrial fibrillation: a meta-analysis of embolic and bleeding complications

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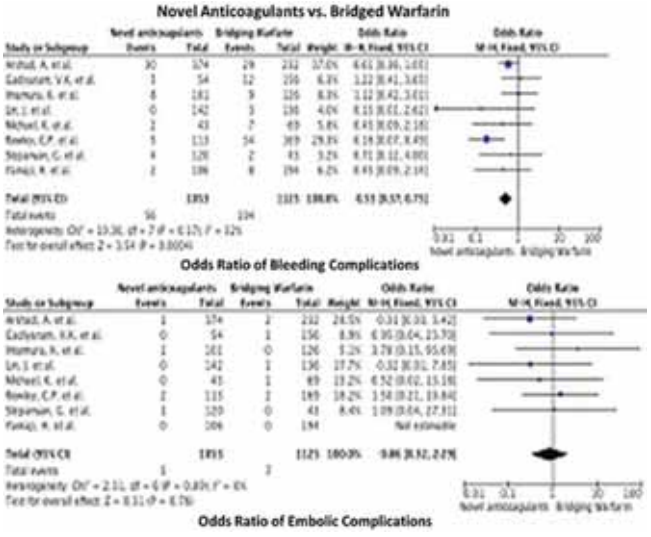
Introduction: Warfarin interruption with heparin bridging (WB) peri-atrial fibrillation (AF) ablation is considered an acceptable option in the most recent HRS guidelines. However, novel oral anticoagulants (NOACs) are increasingly used. There have been some concerns raised about the safety of NOACs in this setting; however, individual studies may be too small to accurately compare anticoagulation strategies given low procedural complication rates. Thus, larger data sets would be very informative.
Methods: We conducted a meta-analysis of all published papers (n=3) and abstracts (n=5) to date that compared complication rates for peri-AF ablation use of NOAC vs. WB. Bleeding complications included pericardial effusion, groin hematoma, GI bleeding and embolic complications included stroke/TIA or systemic embolism. We used the Mantel-Haenszel fixed effect model for pooling the study results, with a random effects model for heterogeneous samples/results.
Results: The 1053 pts on a NOAC (91% dabigatran) were similar to the 1125 pts on WB. NOAC were stopped 2.5-96 hrs pre-procedure and restarted 1-48 hrs post-procedure. Composite bleeding rates were significantly lower in NOAC pts (5.32%) vs WB pts (9.24%), (OR 0.53, 95% CI 0.37-0.75; I2 = 32%). This was driven by significant decrease in minor bleeding complications. Composite embolic rates were similar in both groups (0.47% in NOAC vs 0.62% in WB, OR 0.86, 95% CI 0.32-2.29; I2 = 0%; Figure)



Conclusions: This meta-analysis suggests that NOAC may be preferable to WB for peri-AF ablation anticoagulation. They are associated with a decrease in bleeding and no significant increase in embolic events compared to WB.

P6279 | BEDSIDE
The morphology and decreased flow velocity of left atrial appendage are strong predictors of stroke in nonvalvular atrial fibrillation

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Introduction: Left atrial appendage (LAA) is an important source of thromboembolism in patients with atrial fibrillation (AF). However, the remodeling of LAA in nonvalvular AF patients with stroke is not completely revealed. This study evaluated whether LAA morphology is related with stroke and LAA flow velocity (LAAV) in nonvalvular AF patients.
Methods: In 238 AF patients, transesophageal echocardiography and cardiac computed tomography were performed. The dimension, morphology and flow velocity of LAA were compared in nonvalvular AF patients with (stroke group, n=67, mean age 66.0±9.3 years) and without ischemic stroke (no-stroke group, n=151, mean age 55.9±10.0 years). LAA morphologies were divided into chicken-wing vs. other types including cauliflower, windsock and cactus.
Results: Compared with no-stroke group, the stroke group had larger LA dimension (4.7±0.8 vs. 4.2±0.6 cm, p=0.001), larger LAA orifice area (4.5±1.5 vs. 3.0±1.1 cm^2, p<0.001), and slower LAA flow velocity (36.3±19.1 vs. 54.7±19.8 cm/s, p<0.001). Patients with chicken-wing type LAA (n=101) had lower proportion of stroke than those with other type LAA (n=137) (18%, vs. 40%, p<0.001). LAA flow velocity was negatively correlated with LAA orifice size (R= -0.48, p<0.001). Patients with chicken-wing LAA had smaller LAA orifice area (3.6±1.6 vs. 3.2±1.0 cm^2, p=0.012) and higher LAA velocity (55±21 vs. 44±21 cm/s, p<0.001) than those with other type LAA. After adjustment for multiple potential confounding factors including CHA2DS2-VASc score, persistent AF, LAA velocity, LAA morphology other than chicken-wing was found to be significant risk factor of stroke (OR 2.9, 95% CI 1.5-6.0, p=0.003).
Conclusion: LAA morphology was closely related with stoke. This finding might be explained by the change of orifice enlargement and LAA flow velocity according to the LAA morphology.

P6280 | BEDSIDE
Clinical management and outcome of major bleeding in patients on oral anticoagulant treatment: results from the climbing study

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Background: The incidence of major bleeding (MB) is about 3% per year in patients on oral anticoagulant treatment. The optimal treatment of oral anticoagulation-induced MB and its effect on clinical outcome remain unclear.
Methods: Patients on oral anticoagulant treatment admitted to the Emergency Department for major bleeding (MB) were included in a prospective, cohort study (CLIMBING). Major bleeding was defined according to ISTH definition. The primary outcome of the study was death occurring during the hospital stay. Secondary outcomes were major thromboembolic complications (acute coronary syndrome, ischemic stroke, systemic cardioembolism, and pulmonary embolism).
Results: As for February 1st, 2014, 312 patients were included in this study, 186 with intracranial hemorrhage (ICH). All patients were on treatment with vitamin K antagonists.
HASBLED ≤3 (OR 4.00; 95% CI 1.99-8.04), and trauma (OR 5.04; 95% CI 2.80-9.06) were independently associated with ICH while active cancer (OR 5.01; 95% CI 1.93-13.01), ischemic heart disease (OR 1.81; 95% CI 1.02-3.23) and high

INR (OR 1.24; 95% CI 1.07-1.43) were independently associated with non-ICH MB. Among HASBLED items, previous stroke (OR 2.16; 95% CI 1.07-4.34; p 0.03) was independently associated with ICH while abnormal renal function (OR 2.13; 95% CI 1.18-3.85; p 0.01), previous bleeding (OR 4.15; 95% CI 1.92-8.95; p<0.001), antiplatelet (OR 3.31; 95% CI 1.19-9.18; p 0.02) and NSAIDS usage (OR 13.69; 95% CI 1.38-135.91; p 0.02) were independently associated with non-ICH MB.
PCCs were most commonly used in patients with ICH (52 vs. 24%, p<0.001) while fresh frozen plasma was most commonly used in patients with non-ICH MB (19 vs 7%; p 0.001).
In-hospital death occurred in 68 patients (21%). ICH (OR 4.28; 95% CI 1.90-9.66; p<0.001), trauma (OR 2.09; 95% CI 1.06-4.15; p 0.03) and re-bleeding during the hospital stay (OR 4.13; 95% CI 1.99-8.58; p<0.001) were independent predictors of in-hospital death while INR at admission, time to INR normalization and HAS-BLED (or any of its items) were not. Of the 312 study patients, 7 had an acute coronary syndrome (2 ICH patients), 5 an ischemic stroke (3 ICH patients), and 4 a pulmonary embolism (3 ICH patients) during the hospital stay. The incidence of thromboembolic complications was 7% in patients receiving and 3.6% in those not receiving PCCs.
Conclusions: Among patients with MB while on oral anticoagulant treatment the risk for death is not associated with HASBLED score. The association between thromboembolic complications and PCCs use need further evaluation.

P6281 | BEDSIDE
Long term follow-up in patients with atrial Fibrillation under 55 years old: Can we predict mortality?

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Atrial fibrillation in young patients is no so common; incidence is below 0.5% depending on the age group considered. Compared to older patients differences are numerous.
They have less co-morbidities, and a lower incidence of thrombo-embolic and bleeding. In the young AF is most often paroxysmal and mortality is lower.
Our objective was to evaluate mortality in young patients with diagnosed AF and a extended follow-up, particularly the relationship with thrombo-embolic risk scores and the type of AF.
Patients and methods: We studied 399 patients who were diagnosed with AF below age 56. The population belongs to our AF-cohort of 3196 patients, which started on Nov-1995. Data was collected until Jan-2014. Demographics, EHRA symptoms, co-morbidities, medication and the CHA2DS2VASc score, type of AF at the first consult and at the last consultation were annotated as well as complications, hospital admissions and mortality.
Results: Mean age was 45±9 (range 17-55 years), with a mean follow up of 98±52 (8-229 months), ten patients were lost to follow-up. 22% of the patients were females.
A CHA2DS2VASc score equal or above 2 was calculated in 28% of the population. 53% presented with paroxysmal AF, 42% with persistent and 3.5% with permanent AF. On the last evaluation 51% had paroxysmal, 23% persistent and 24% permanent AF.
27 (6.9%) patients died, the Kaplan-Meier survival curves showed that a CHA2DS2VASc below 2 was significantly associated with survival. We also observed that the progression to permanent AF was significantly associated with mortality. When we combined both variables the survival curves were significantly different.
Conclusion: In young patients with AF, the combination of a high CHA2DS2VASc score and the progression to permanent AF appears to have a detrimental effect on survival.

P6282 | BEDSIDE
The prognostic significance of cardiac structure and function in atrial fibrillation: the ENGAGE AF-TIMI 48 Echocardiographic Substudy

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Purpose: Atrial fibrillation (AF) is associated with increased risks for thromboembolism and death. However, the associations between cardiac structure and function and adverse outcomes in AF are less well understood.
Methods: The ENGAGE AF –TIMI 48 study tested the oral factor Xa inhibitor edoxaban in comparison to warfarin for the prevention of stroke (ischemic or hemorrhagic) or systemic embolism in 21,105 subjects with nonvalvular AF and CHADS2 ≥2. In a prospective substudy of 971 subjects who underwent transthoracic echocardiography at baseline, we used Cox proportional hazards models to evaluate the associations between cardiac structure and function and the risks for cardiovascular death and thromboembolism (ischemic stroke, TIA, or systemic embolism).
Results: Over a median follow up of 2.5 years, 64 (6.6%) cardiovascular deaths and 48 (4.9%) incident thromboembolic events occurred in 971 patients. In models adjusted for CHADS2 score, aspirin use, and randomized treatment, larger LV end diastolic volume index (HR: 1.45 [95%CI: 1.08,1.93] per 1 SD [12.9 ml/m^2]) and higher LV filling pressures measured by E/'e (HR: 1.31 [95%CI: 1.03,1.67] per 1 SD [4.6]) were independently associated with increased risks for cardiovascular death. No features of cardiac structure and function were independently associated with thromboembolism. Findings were similar with adjustment for CHA2DS2-VaSc score.
Conclusions: In a contemporary AF population, increased LV size and filling pressures were significantly associated with increased risk for cardiovascular death. Cardiac structure and function may help stratify AF patients for adverse outcomes.

MECHANISMS IN ATRIAL FIBRILLATION

P6284 | BEDSIDE
Paroxysmal and chronic atrial fibrillation: the role of endothelial dysfunction

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Purpose: Atrial fibrillation (AF) is a common encountered disorder associated with various cardiovascular diseases. Measurement of endothelial function is well validated in large population studies as strong predictor of adverse cardiovascular outcomes. Although paroxysmal AF usually evolves to chronic AF, the role of endothelial dysfunction remains undetermined.
Methods: In this cohort study we enrolled 152 consecutive subjects with AF. Thirty five subjects had paroxysmal AF and 117 chronic (long standing persistent or permanent) AF. Flow mediated dilation (FMD) was measured as an index of endothelial function. All subjects underwent two-dimensional echocardiographic assessment. Left ventricle ejection fraction (LVEF) was calculated based on biplane method of discs, left ventricle mass index to body surface area (LVmass/BSA) was calculated with the method of Devereux (prolate ellipse), left atrial diameter index to body surface area (LAdiam/BSA) was measured in the parasternal long axis view and left atrial volume index to body surface area (LAvol/BSA) was measured based on biplane Simpson's rule.
Results: Subjects with chronic AF compared to subjects with paroxysmal AF were older (73±10 years vs. 66±15 years, p=0.002), had impaired LVEF (44±14% vs. 53±9%, p=0.001) increased LAdiam/BSA (26±4mm/m^2 vs. 20±3mm/m^2, p<0.001), increased LAvol/BSA (41±9.6ml/m^2 vs. 29±7.7ml/m^2, p<0.001), increased LVmass/BSA (116±35 gr/m^2 vs. 99±29 gr/m^2, p=0.06) and impaired creatinine clearance (64±18 ml/min/1.73m^2 vs. 83±20 ml/min/1.73m^2, p=0.001). Importantly, subjects with chronic AF had impaired FMD compared to subjects with paroxysmal AF (4.09±1.67% vs. 6.83±1.38% p<0.001). In addition, there was an inverse correlation between FMD and LAdiam/BSA (r=-0.53, p<0.001), LAvol/BSA (r=-48, p<0.001), LVmass/BSA (r=-0.364, p=0.007) and a positive correlation between FMD and LVEF (rho=0.30, p=0.003). Interestingly, a linear regression model revealed that subjects with chronic AF had impaired FMD [b=-1.61 95%CI (-2.33 to -0.89), p<0.001] even after adjustment for confounders such as age, sex, LVEF, LVmass/BSA, LAvol/BSA, creatinine clearance, arterial hypertension and the presence of diabetes mellitus.
Conclusion: Endothelial dysfunction is associated with atrial remodeling in patients with AF and is implicated in the progression from paroxysmal to chronic AF.

P6285 | BENCH
Depressed pitx2 levels in patients with 4q25 risk variants is linked to hallmarks of atrial fibrillation such as right atrial myocyte hypertrophy and increased frequency of transient inward currents

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Purpose: Atrial fibrillation (AF) has been associated with 4q25 risk variants that presumably modulate the expression or activity of the transcription factor pitx2. However, the relationship between 4q25 variants, pitx2 levels, and cellular electrophysiological hallmarks of atrial fibrillation remains elusive and we here investigated this issue.
Methods: Perforated patch-clamp technique was applied to right atrial myocytes from humans or atrial chamber-specific pitx2+/– mice in order to measure cell capacitance, ionic currents, or spontaneous action potentials. Protective (CCGG) and risk (non-CCGG) 4q25 variants were identified by DNA sequencing and pitx2 levels were determined with qPCR.
Results: Eight samples with 4q25 risk variants had twofold lower pitx2 levels than ten samples with the protective 4q25 variants. Moreover, myocytes from 13 risk variants without AF had larger cell capacitance than myocytes from 14 patients with the protective variant (79±10 vs. 53±6 pF, p<0.05). Myocytes from AF patients had even larger cell capacitance for both 3 risk (107±10 pF) and 7 protective (103±9 pF) variants. As expected, L-type calcium current amplitude was smaller in patients with than without AF (-1.3±0.3 vs. -2.8±0.3 pA/pF, p<0.01), but there were no differences among risk and protective variants in patients with-

out AF (-2.6±0.4 vs. 3.0±0.4 pA/pF, p=0.5). By contrast, myocytes from the same patients with risk variants had a significantly higher frequency of spontaneous transient inward currents (Iti) than those with the protective variant (1.2±0.4 vs. 0.2±0.1 events/min, p<0.05). Comparison of right atrial myocytes from 6 atrial-specific pitx2+/– and 4 wild type (WT) mice confirmed that partial loss of pitx2 function increases cell capacitance (69±6 vs. 44±5 pF, p<0.05). Moreover, the frequencies of spontaneous membrane depolarizations and Iti were proportional, and spontaneous action potentials were more frequent in pitx2+/– than in WT (1.7±0.7 vs. 0.2±0.1 events/min, p<0.05). In addition, the voltage threshold for spontaneous AP firing was shifted from -60±5 mV in WT to -75±3 mV in pitx2+/– (p<0.05).
Conclusions: Patients with 4q25 risk variants have reduced pitx2 levels and right atrial myocytes from those without AF already have cellular electrophysiological hallmarks of AF such as increased size and Iti frequency. These features are reproduced in heterozygous pitx2+/– mice, demonstrating that pitx2 deficiency in 4q25 variants increase the risk of arrhythmogenic afterdepolarizations.

P6286 | SPOTLIGHT
New inflammatory predictors for non-valvular atrial fibrillation: echocardiographic epicardial fat thickness and neutrophil to lymphocyte ratio

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Objectives: The objective of this study was to investigate the relationship of echocardiographic epicardial fat thickness (EFT) and neutrophil to lymphocyte ratio (NLR) with different types of non-valvular atrial fibrillation (AF) in a clinical setting.
Methods: A total of 197 consecutive patients were enrolled in the study. Seventy-one patients had paroxysmal non-valvular AF, 63 patients had persistent/permanent non-valvular AF, and 63 patients had sinus rhythm (control group). EFT was measured with echocardiography, while NLR was measured by dividing neutrophil count by lymphocyte count.
Results: EFT was significantly higher in patients with paroxysmal non-valvular AF compared with those in the sinus rhythm group (6.6±0.7 mm vs. 5.0±0.9 mm, p<0.001). Persistent/permanent non-valvular AF patients had a significantly larger EFT compared with those with paroxysmal AF (8.3±1.1 mm, vs. 6.6±0.7 mm, p<0.001). EFT had a significant relationship with paroxysmal non-valvular AF (odds ratio:4.672, 95% CI: 2.329 to 9.371, p<0.001) and persistent/permanent non-valvular AF (OR 24.276, 95% CI: 9.285 to 63.474, p<0.001).NLR was significantly higherin those with paroxysmal non-valvular AF compared with those in the sinus rhythm group (2.5±0.6 vs. 1.8±0.4, p<0.001). Persistent/permanent non-valvular AF patients had a significantly larger NLRwhen compared with paroxysmal non-valvular AF patients (3.4±0.6, vs. 2.5±0.6, p<0.001). NLR (>2.1) had a significant relationship with non-valvular AF (OR: 11.313, 95% CI: 3.025 to 42.306, b: 2.426, p<0.001).
Conclusion: EFT and NLR are highly associated with types of non-valvular AF independent of traditional risk factors. EFT measured by echocardiography and NLR appears to be related to the duration and severity of AF.

P6287 | BENCH
Increased atrial fibrillation susceptibility in mice with myocardial specific NOX2 overexpression is prevented by short term statin treatment

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Rationale: Myocardial oxidative stress and inflammation are associated with the electrical and structural atrial remodeling induced by atrial fibrillation (AF). We have previously shown that a NOX2-containing NADPH oxidase (NOX2) is the main source of reactive oxygen species (ROS) in the atrial myocardium. Atrial NOX2 activity is increased early after pacing-induced AF in the goat and is an independent predictor of postoperative AF in patients undergoing cardiac surgery.
Aims: To establish whether an increase in atrial NOX2 activity is in itself sufficient to generate an atrial substrate for AF, we have assessed cardiac structure and function (by echocardiography/tissue Doppler), electrocardiographic properties and AF inducibility (by transoesophageal electric stimulation) in cardiomyocyte-specific NOX2 Tg mice. As statins inhibit NOX2 activity (by preventing the isoprenylation of Rac), we then repeated these investigations in NOX2 Tg and WT littermates that had been allocated to either atorvastatin (ATV 30 mg/kg/day) or placebo for 2 weeks. All measurements were carried out by investigators blinded to treatment allocation.
Methods and results: NOX2 Tg mice show a modest increase in myocardial superoxide production (+16%, n=4/group, P<0.05) and have normal atrial and LV size and function with no difference in collagen content. Basal electrocardiographic parameters did not differ between genotypes; however, both the probability of inducing AF (19±2.2% in Tg vs. 9±1.8% in WT, n=20/group, P<0.01) and the duration of the AF episodes were significantly increased in NOX2 Tg. Treatment with ATV abolished the difference in AF inducibility/duration between genotypes. Atrial IL-1β expression was significantly raised in NOX2 Tg, in keeping with a pro-inflammatory effect of ROS; ATV treatment also abolished the difference in IL-1β expression.
Conclusions: Myocardial NOX2 overexpression is sufficient to increase AF susceptibility and myocardial pro-inflammatory profile in mice, which are reversed by 2-week ATV treatment. Taken together, our findings suggest that, by inhibiting myocardial NOX2 activity and related inflammation, statin treatment may decrease the incidence of post-operative AF (currently under investigations NCT01573143) and prevent early AF-induced electrical remodeling.

P6288 | BEDSIDE
CC genotype of VKORC1 is associated with haemostatic disorders in patients with atrial fibrillation

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Purpose: To identify associations between genetic polymorphisms of VKORC1 C1173T and haemostatic indicators in patients with atrial fibrillation.
Methods: Studied were 200 patients with ischemic heart disease and permanent atrial fibrillation (mean age 64±9.8 years). All the patients were divided into three groups: 1 group comprised 66 patients with CC genotype, 2 group - 68 patients with CT genotype and 3 group - 66 patients with TT genotype of VKORC1. Patients of all groups were age and sex matched. We evaluated haemostatic indicators such as thrombin activatable fibrinolysis inhibitor (TAFI), fibrinogen, antithrombin, soluble fibrin-monomer complexes (SFMC) and ADP-platelets aggregation.
Results: We found significant associations between CC genotype of VKORC1 and TAFI (R=0.44; p=0.01), SFMC (R=0.35; p=0.02) and ADP-platelets aggregation (R=0.3; p=0.02). In patients with CC genotype of VKORC1 the odds ratio for TAFI levels more than 205% was 1.3 (95% CI: 1.1-1.7; p=0.03), SFMC more than 10 mg% - 1.2 (95% CI: 1.02-1.5; p=0.02), ADP platelets aggregation beginning time less than 11 seconds - 1.1 (95% CI 1.01-1.8; p=0.04).
Conclusion: In patients with permanent atrial fibrillation CC genotype of VKORC1 is associated with coagulation cascade activation, decreasing of fibrinolytic system activity and increasing of platelets aggregation.

P6289 | BEDSIDE
Role of masked coronary heart disease in patients with recent onset atrial fibrillation and troponin elevations

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Background: Patients with recent onset atrial fibrillation (AF) and troponin (cTnI) elevations show poor outcomes. Coronary heart disease (CHD) might be cause, consequence or innocent bystander.
Objective: To recognize and treat CHD to avoid adverse events.
Methods: Patients with recent onset AF participated in the study. The exclusion criteria were acute coronary syndrome and severe comorbidities. Patients managed with standard care (Group 1, n=1086, 2010-2011 years) were compared to patients managed with tailored care inclusive of echocardiography and stress testing when required (Group 2, n=1055, 2012-2013 years).
End-point: The composite of ischaemic vascular events inclusive of stroke, acute coronary syndrome, revascularization and cardiovascular death at six-month follow-up.
Results: Out of 4008 patients considered, 2141 with recent onset atrial fibrillation were enrolled; 183 showed cTnI elevations, 92 in group 1 and 91 in group 2. At univariate analysis abnormal cTnI elevations, known coronary heart disease, age, hypercholesterolemia, diabetes mellitus were independent predictors of the primary end-point. However, only cTnI elevations, known ischaemic heart disease and age were predictors of the end-point at multivariate analysis. Overall 2 versus 7 patients in group 1 and 2, respectively, (p=0.033), underwent revascularisation. Eventually, 16 patients in group 1 versus 5 patients in group 2 reached the end-point (p=0.019; table). Patients of group 2 were managed as follow: 35 were admitted of whom 15 with positive stress testing and 20 with high cTnI values (mean values: 0.64±1.01 ng/mL). Fifty-six patients were discharged with negative stress testing (n=13) or very low cTnI values (n=43, mean values 0.29±0.30 ng/mL).

Primary composite end-point

	Primary endpoint at six months			
	Total	Stroke	CHD	Death
Group 1 (n=92)	16 (17.4%)	4 (4.3%)	10 (11%)	3 (3.3%)
Group 2 (n=91)	5 (5.5%)	1 (1.1%)	4 (4.4%)	2 (2.2%)
p value	0.019	0.368	0.163	1.0

CHD, coronary heart disease; Death, cardiovascular death.

Conclusions: In patients with AF and cTnI elevations, tailored care inclusive of echocardiography and stress testing succeeded in recognizing and treating "critical" masked CHD avoiding adverse events.

P6290 | BEDSIDE

Left atrial phasic functions and plasma NT-proBNP levels predict atrial fibrillation development in patients with hypertrophic cardiomyopathy: A prospective follow-up study

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Purpose: Atrial fibrillation (AF) is the most common arrhythmia in patients with hypertrophic cardiomyopathy (HCM) and associated with morbidity. NT-pro-BNP levels are shown to be elevated in patients with HCM. We investigated if left atrial (LA) phasic functions and plasma NT-proBNP levels could predict future development of AF in patients with HCM.
Methods: Seventy patients with HCM who were in sinus rhythm at the time of their recruitment were enrolled. The following LA volumes (LAVs) were measured by Simpson's rule: maximal volume (Vmax) during left ventricular (LV) end-systole, minimal volume (Vmin) just before mitral valve closure and LA volume before atrial contraction (VpreA) at the onset of the P wave on the simultaneously recorded ECG. Left atrial total emptying fraction (LATEFr), LA active emptying fraction (LAAEFr), LA passive emptying fraction (LAPEFr) were calculated by using these LAVs. LV mass index (LVMI) was calculated by the method of Devereux. E/E' ratio of the LV septal wall (E/E' septal) was obtained to characterize LV filling by using tissue Doppler. NT-pro-BNP levels of the patients were measured on the same day with echocardiographic study.
Results: The patients were followed up for 37.1±1.9 months. During follow-up 16 patients (8 men, 54.8±12.05 years) developed AF. When patients with AF (group 1) were compared with the ones without AF (group 2, n=54) significant differences were observed between groups in terms of LAEF (p=0.002), LAVI (p<0.001), LAAEFr (p=0.005), E/E' septal (p=0.035), LVMI (p=0.032) and logNT-proBNP (p=0.004). In multivariate analysis LAVI (odds ratio [OR], 1.04; 95% confidence interval [CI]: 0.99-1.09; p=0.002), LAAEFr ([OR], 0.99; 95% [CI]: 0.89-1.08; p=0.007), LATEFr ([OR], 1.01; 95% [CI]: 0.89-1.13; p=0.018) and NT-proBNP levels ([OR], 4.25; 95% [CI]: 0.68-26.71; p=0.005) predicted AF development. An NT-proBNP cut-off value of 980 pg/mL predicted future AF occurence with 72% specificity and 83% sensitivity [AUC=0.772 (95% CI: 0.651-0.893)]; a LATEFr cut-off value of 49% with 63% specificity and 76% sensitivity [AUC=0.755 (95% CI: 0.63-0.879)]; a LAAEFr cut-off value of 34% with 63% specificity and 74% sensitivity [AUC=0.732 (95% CI: 0.578-0.887)]; a LAVI cut-off value of 48 mL/m^2 with 72% specifity and 88% sensitivity [AUC=0.818 (95% CI: 0.707-0.93)].
Conclusion: In patients with HCM, LA reservoir and pump functions and plasma NT-proBNP levels predict AF development. This observation might be helpful in early detection of patients who are prone to AF development.

P6291 | BENCH

Degree of fatty infiltration contributes to complexity of the substrate for atrial fibrillation in goat left atria

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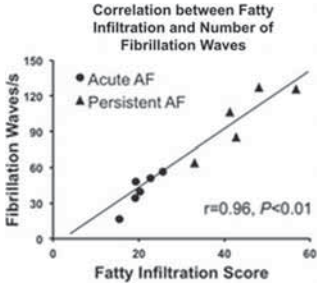
Purpose: Progression of atrial fibrillation (AF) is caused by electrical and structural remodeling. Fibrosis and altered connexin expression are known alterations in atrial tissue structure contributing to the development of an AF substrate. To date, the effect of fatty infiltration on AF conduction has not been studied. We hypothesize that the degree of fatty infiltration is an important determinant of AF progression and AF complexity in goat left atria (LA).
Methods: LA epicardial high-density contact mapping (256 electrodes) was performed in goats with acutely induced (aAF, n=6) and persistent AF (persAF, n=5). After analysis of unipolar AF electrograms, AF cycle length (AFCL) and number of fibrillation waves per second (waves/s) were quantified. Mapped tissue regions were excised and reconstructed by high-resolution MRI (voxel size [78×78×78]μm^3), allowing myocardial fat quantification within the atrial wall using a Fatty Infiltration Score (FIS, quantification of proportion fat per electrode grid).
Results: AFCL (ms) was shorter in persAF than in aAF (103±20 vs. 127±15, P<0.05) and waves/s were higher in persAF than in aAF (102±27 vs. 41±14, P<0.01). The degree of fatty infiltration was much higher in persAF than aAF (FIS=44.3±8.7 vs. FIS=20.4±3.5, P<0.01). Waves/s correlated well with fatty infiltration across (bivariate r=0.96, P<0.01; see Figure) & corrected for the 2 groups (partial r=0.87, P<0.01). AFCL correlated inversely with fatty infiltration (r=-0.81, P<0.01).
Conclusion: Persistence of AF is associated with fatty infiltration in goat left atria. Fatty infiltration seems to be an important determinant of AF complexity that deserves further targeted investigation.



P6292 | BENCH

Vidarabine, an anti-herpesvirus agent, prevents catecholamine-induced atrial fibrillation in mice

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Objectives: Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice. In recent years, catecholamine-induced hyperphosphorylation of cardiac ryanodine receptor (RyR) and oxidative stress, which is related to the "leaky" RyR, have been considered to play an important role in arrhythmogenesis. The usefulness of beta-adrenergic receptor (β-AR) antagonist (β-blocker) for the treatment of catecholamine-induced AF is established. Adenylyl cyclase (AC) plays a critical role in β-AR mediated signaling. Previously, we found that Vidarabine, an anti-herpesvirus agent, is a selective inhibitor of cardiac AC. Here, we evaluated the anti-arrhythmic effect of Vidarabine using our mouse model of AF induced by transesophageal atrial burst pacing.
Methods and results: After treatment with Vidarabine (15 mg/kg/day) or Metoprolol (a β-blocker) (4 mg/kg/day) via subcutaneously implanted osmotic minipump for 6 days, we assessed the duration of AF in mice. The transesophageal atrial burst pacing reproducibly induced self-terminating AF. Sympathetic activation by intraperitoneal administration of norepinephrine (NE) (1.5 mg/kg), strikingly elongated the duration of AF (control 39 sec vs NE 739 sec, P<0.001). Both Vidarabine and Metoprolol shortened the duration of NE-elongated AF (control 674 sec vs Vidarabine 364 sec, P<0.05; vs Metoprolol 167 sec, P<0.05). Metoprolol significantly decreased left ventricular ejection fraction even at the lower dose (3 mg/kg/day for 2 days), whereas Vidarabine did not affect them. Vidarabine blunted the NE-induced RyR phosphorylation in atria (~20% and ~25% lower than vehicle-treated control at Ser 2808 and Ser 2814, respectively, P<0.05). In atrial myocytes, Vidarabine attenuated isoproterenol (ISO)-enhanced diastolic Ca2+ leak from sarcoplasmic reticulum (SR) (~27% lower than myocytes without Vidarabine treatment, P<0.05) and spontaneous Ca2+ release (~57% lower, P<0.01). Meanwhile, ISO increased the production of reactive oxygen species in neonatal rat cardiomyocytes. Intraperitoneal administration of Tempol (24 mg/kg), a superoxide dismutase mimetic, inhibited NE-elongated AF (~66% shorter than control, P<0.05). Interestingly, co-administration of Vidarabine and Tempol had no additive inhibitory effect on the NE-elongated AF, indicating that Vidarabine may suppress NE-elongated AF through antioxidative mechanisms.
Conclusions: These results indicate that Vidarabine inhibits AF via suppressing diastolic Ca2+ leak from SR without deterioration of heart function. The amelioration of oxidative stress may be involved in the mechanism.

P6293 | BENCH

Fluctuation in QT interval at onset and termination of paroxysmal atrial fibrillation

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Purpose: To compare the QT interval before, during and after episodes of paroxysmal atrial fibrillation (PAF).
Methods: A total of 35 patients (age 53±12 years, 48% female) who had documented PAF on Holter monitoring were enrolled. QT interval was measured at: SR immediately prior to the onset and after the termination PAF episodes (SRbaseline and SRpostAF respectively) and during AF.QTc was calculated in all patients by using three formulas: Bazett's, Fridericia and Framingham.
Results: None of the patients was on drug that altered QT interval.QTc was longer during AF comparing to that during SR (SRbaseline and SRpostAF). QTc-SRpostAF was shorter than QTc-SRbaseline (Table 1). QTc shortening during SR[QTc (SRbaseline-SRpostAF)] was positively associated with the QTc-SRbaseline but reversely correlated to the QTc prolongation during AF (Fig. 1), which showed concordant change with different formulas applied.

Table 1

	$SR_{baseline}$	AF	SR_{postAF}	P value ($SR_{baseline}$ vs. SR_{postAF})	P value ($SR_{baseline}$ vs. AF)
Bazetts	435±34ms	503±69ms	407±38ms	0.001	0.001
Fridericia	423±31ms	454±53ms	397±31ms	0.001	0.05
Framingham	422±30ms	449±44ms	393±35ms	0.001	0.05
P value (Bazett's vs. Fridericia vs. Framingham)	0.032	0.016	0.012	–	–

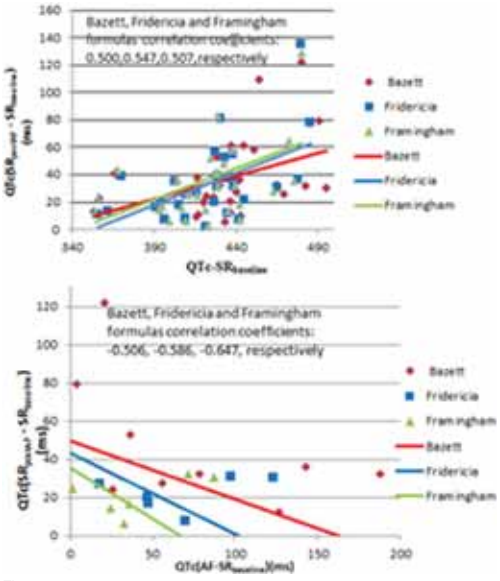

Figure 1

Conclusion: QTc is prolonged during PAF comparing to that during preceding SR, then shortened after index AF episode terminates and becomes shorter than the QTc during SR prior to AF. The results suggest a shortening of ventricular repolarization time after a prolongation of QTc during the preceding AF.

P6294 | BEDSIDE

Incidence and predictors of new-onset atrial fibrillation in septic shock patients in a medical ICU: data from 7-day Holter ECG monitoring

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Objectives: New-onset atrial fibrillation (NAF) is a common complication of septic shock and incidence is underestimated. We sought to investigate the real incidence, associated risk factors for NAF, and its prognostic impact during septic shock in patients hospitalized in a medical Intensive Care Unit (ICU).
Design: Prospective, single-center, observational study.
Setting: Medical ICU in a large university teaching hospital.
Patients: All consecutive patients presenting between March 2011 and May 2013 with septic shock were eligible for inclusion, with the following exclusion criteria: patients aged <18 years, prior history of AF (paroxysmal or sustained), and patients transferred from another ICU with prior septic shock.
Intervention: After inclusion, all patients were equipped with long-duration Holter ECG monitoring for 7 days.
Measurements and Main Results: NAF was defined as an AF episode lasting more than 30 seconds. Patient characteristics, infection criteria, cardiovascular parameters, severity of illness, medical and technical support therapies were recorded.
Among 66 patients, 29 (44%) developed NAF; 10 of which (34%) would not have been diagnosed without Holter ECG monitoring. NAF patients were older, and more often presented markers of heart failure, i.e. higher troponin and NT-proBNP levels associated with lower left ventricular ejection fraction (LVEF), as compared to patients who remained in sinus rhythm. NAF patients also had longer QRS duration and more often presented nonsustained supra ventricular arrhythmias (<30s) on the first day. In a multivariate model, only age (OR: 1.06; p=0.01) and LVEF<45% (OR: 13.01, p=0.03) remained associated with the occurrence of NAF. However, NAF was not an independent predictor of 28 or 90 day mortality.
Conclusion: This is the first study to examine the exact incidence and risk factors of NAF in septic shock patients. NAF is common, especially in older patients, and is associated with low ejection fraction. We did not find NAF to be independently associated with higher mortality in this study.

ENDOTHELIAL FUNCTION – BASIC II

P6296 | BENCH

Are there gender difference in endothelial progenitor cell number and function and the effect with thymosin beta-4 treatment?

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Purpose: There are gender differences in incidence and progression of cardiovascular disease (CVD). Since endothelial dysfunction is associated with CVD, there may be gender-related difference in endothelial progenitor cells (EPCs). We aim to correlate EPCs with Framingham risk score (FRS) and hypothesize that treatment of human EPCs with thymosin beta-4 (Tβ4), a novel peptide may improve EPC number and function.
Methods: We recruited 76 age-matched subjects from outpatient cardiology clinic (male, 64±11 years, n=53; postmenopausal female, 65±12 years, n=23). Peripheral blood mononuclear cells were isolated using Ficoll density gradient centrifugation and grown on fibronectin-coated plates. EPCs were counted using flow cytometry of CD34+ and KDR+ markers. Colony forming unit (CFU) assay was performed to determine EPC function. EPCs were treated with Tβ4 (1000ng/mL) for 3 days.
Results: Despite the significantly lower FRS in female, EPC number (%CD34+/KDR+) and function (CFU) were not statistically different between genders (Table 1). We also did not establish a significant association between FRS and CFU (r=-0.28; r=-0.25; P>0.05) and with EPC number (r=-0.25; r=-0.22; P>0.05) in either male or female subjects. In male subjects, Tβ4 treatment increased the EPC function by 8% (14.6±2.3). This improvement was similar compared to Tβ4-treated CFU from female subjects (15.0±3.2) (P>0.05).

Table 1. Baseline clinical characteristics and endothelial progenitor cell number and function of recruited subjects

	Male (n=53)	Female (n=23)	P-value
Age, years	64±11	65±12	NS
BMI, kg/m^2	26±4	25±4	NS
Systolic blood pressure, mmHg	132±17	130±13	NS
Average 10 year Framingham risk, %	9	5	0.001
Diabetes, %	49	48	NS
Hypertension, %	81	83	NS
CD34$^+$/KDR$^+$, %	0.41±0.05	0.42±0.03	NS
Colony forming unit (CFU), n	13.5±2.5	14.3±3.5	NS

Conclusions: EPC number and function were not significantly different between genders, despite the higher Framingham risk score observed in male subjects. Tβ4 treatment improved EPC function in both genders.

P6297 | BENCH

Role of Angptl4 in cardioprotection of Rosuvastatin in reperfused diabetic hearts

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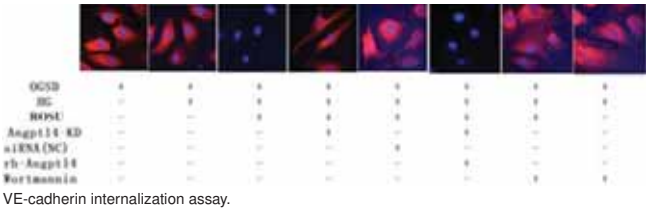
Purpose: Functional disruption of microvascular barrier caused by ischemia/reperfusion results in ischemia/reperfusion injury (IRI). Hyperglycemia may aggravate myocardial IRI since it worsens the barrier function. Angiopoietin-like 4 (ANGPTL4) has the potential to improve endothelial barrier function and may be involved in reperfused diabetic heart protection. To confirm the effect of ANGPTL4 in ROSU-mediated cardiac protection, studies in vitro and in vivo were conducted.
Methods: HCMECs were cultured in normal (5.5mM) and high glucose (18mM) for 48h respectively followed by glucose-oxygen-serum deprivation (GOSD) for 2h and reoxygenation for 2h. RhAngptl4 (1μg/ml), PPARα inhibitor MK886 (1mM) were supplemented. HCMECs apoptosis was detected by TUNEL. Endothelial monolayer permeability was assessed.VE-cadherin internalization was detected by confocal microscope. ZDF rats underwent 45min ligation and 3h reperfusion. SiRNA was used to knock-down Angptl4 expression in rat hearts. High permeability size and infarct size were determined by FITC-dextran and TTC staining.
Results: HCMECs apoptosis significantly increased after the GOSD/ reoxygenation treatment in a time and glucose concentration-dependent manner. Compared with control, ROSU dramatically decreased HCMECs apoptosis (21%±5 vs. 56%±6), fluorescence intensity (1925±136 vs. 3560±182) and VE-cadherin internalization.These protective effects of ROSU were inhibited by MK886. ROSU markedly reduced size of hyperpermeability (24%±2 vs. 35%±6) and infarction (41%±6 vs. 56%±8) of ZDF rats in AMI/reperfusion model compared with control.



VE-cadherin internalization assay.

Conclusions: ROSU protects reperfused diabetic heart through attenuating HCMECs apoptosis and paracellular hyperpermeability.This protection may be related to ROSU-mediated upregulating of Angptl4 via PPARα pathway.

P6298 | BENCH
Endothelial cell functions are differentially affected by shed microvesicles and exosomes in coronary artery disease

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Background and purpose: Shed microvesicles (SMV) and exosomes are released from cells by different mechanisms. Thus, quantitative as well as qualitative changes of each particle population in patients with coronary artery disease (CAD) may reflect an altered activation status of the endothelium, platelets and leukocytes. Moreover, SMV and exosomes might exert differential effects on the endothelium. Yet, alterations in both populations have not been studied side-by-side so far.
The aim of the present study was therefore to compare the impact of SMVs and exosomes from healthy subjects and CAD patients on endothelial cell (EC) functional characteristics, thought to be important in atherosclerotic vascular disease.
Methods: Exosomes and SMVs were isolated from plasma of patients with stable CAD and age-matched healthy control (HC) subjects (n=34-44 per group) by stepwise filtration and ultracentrifugation (particle identity verified by electron microscopy and dynamic light scattering). Functional effects of vesicle fractions on cultured human arterial ECs were analyzed. In parallel, levels of total, platelet-derived (PMVs), endothelial-derived (EMVs) and leukocyte-derived (LMVs) SMVs were assessed by flow cytometry. Moreover, the impact of therapeutic approaches, i.e. changes in vesicle counts and their functional effects, were monitored in patients with CAD randomized into optimal medical treatment (OMT; n=15) or by OMT with an additional a supervised exercise program (ET; n=18).
Results: In CAD patients, plasma counts of EMVs and LMVs ($p<0.05$ vs. con for both), but not of PMVs or total SMVs were increased versus HC. SMVs of HC, but not of CAD patients supported in vitro re-endothelialisation (by 30±10% and 9±9% vs. PBS, respectively, $p<0.05$). ET, but not OMT, improved CAD SMV capacity to support in vitro re-endothelialization (by 30±12%, and 16±14% vs. begin, respectively, $p<0.05$). Over the whole study population, LMV plasma count was negatively correlated with overall SMV effect on re-endothelialization ($p=0.0001$, $r=-0.53$). Exosomes of CAD as well as HC upregulated ICAM-1 (by 19±5% and 21±5%, $p<0.05$) and VCAM-1 (by 31±7% and 29±4%, $p<0.05$) expression by HAEC. Similarly, for EC death, particle type ($p=0.02$), not disease status was determined as source of variation by ANCOVA, indicating a differential biological effect of SMVs and exosomes.
Conclusion: SMVs and exosomes differentially impact on endothelial cell functions. In CAD, SMV capacity to support re-endothelialization was impaired, but partially rescued by exercise training.

P6299 | BENCH
Association of eNOS uncoupling with endothelial dysfunction in atherosclerotic plaques of human arteries

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Purpose: The bioavailability of nitric oxide (NO) determines the function of the endothelium in the vessel wall. Endothelial dysfunction accompanied with decreased availability of NO may occur either because of decreased expression or impaired function of endothelial nitric oxide synthase (eNOS). There are inconclusive experimental and clinical observations showing that eNOS protein levels are decreased, normal or even increased in the endothelium overlying atherosclerotic lesions in arteries. This study was established to determine the exact mechanism underlying decreased NO bioavailability in the endothelium covering atherosclerotic lesions in human arteries.
Methods: Fragments of atherosclerotic and non-atherosclerotic (control) carotid arteries were isolated from patients undergoing carotid endarterectomy. Kinetics of NO/O2-/ONOO- radicals were measured in vitro with highly sensitive electrochemical nanosensors near the surface of a single endothelial cell. Total eNOS mRNA and protein expression was analyzed with the use of quantitative RT-PCR and western blotting. eNOS dimmers and monomers was determined using low-temperature SDS-PAGE electrophoresis under both reducing and nonreducing conditions.
Results: The measurement of NO/O2-/ONOO- radicals revealed reduced release of bioactive NO (214 vs. 556 nmol/L) and increased levels of both O2- (71 vs. 21 nmol/L) and ONOO- (648 vs. 288 nmol/L) after activation of eNOS in endothelial cells from atherosclerotic plaques in comparison to cells from control samples. Interestingly, eNOS mRNA and protein expression was much higher in the endothelium of atherosclerotic arteries (0.15±0.44 arbitrary units) than in control (0.09±0.25 arbitrary units). The determination of the state of functional eNOS with the use of western blot technique revealed a significantly elevated monomer-to-dimmer ratio in cells from atherosclerotic lesions (0.20±0.04) in comparison to control cells (0.01±0.005).
Conclusions: In summary, our data show that endothelial dysfunction in atherosclerotic lesions is associated with decreased level of bioavailable NO and elevated production of O2- and ONOO- after eNOS activation. Although the expression of both eNOS mRNA and protein is enhanced, increased production of O2- and ONOO- may be explained by the disruption of the dimeric structure of the eNOS enzyme.

P6300 | BENCH
Aerobic training increases blood nitric oxide and prevents the impairment in vascular reactivity caused by fructose intake in rats

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Purpose: The high intake of fructose is associated with cardiometabolic disorders. But it is uncertain the effect of fructose overload on vascular reactivity and possible effects of non-pharmacological treatments. Thus, the aim of this study was to investigate the effect of a high-fructose diet on vascular reactivity and the possible effects of aerobic exercise training in rats.
Methods: Wistar rats (n=7x4 groups), males, adults, were divided in Control group (C; tap water), Fructose group (F; water with 10% fructose) for 10 weeks; Control Training group (CT) and Fructose Training group (FT), both same as C and F groups, respectively, adding aerobic training on a treadmill (04 times/week, 50-75% of maximal exercise test) in the last 8 weeks. Body weight and caloric intake were assessed weekly. At the end of treatment were analyzed serum triglycerides (TG), insulin, leptin and isoprostane, nitric oxide (NO - Nitric Oxide Analyzer), invasive blood pressure and heart rate (HR) by femoral canulation and vascular reactivity of thoracic aortic induced by phenylephrine (FNF) and acetylcholine (ACh).
Results: There were no differences in body mass gain, caloric intake, insulin or leptin between groups. TG was higher ($P<0,01$) only in F group (159.6±18.8mg/dL) and was similar between FT (77.9±8.7mg/dL), CT (89.7±10.2mg/dL), and C (83.4±15.2mg/dL) groups. The same pattern was observed for isoprostane: higher ($P<0.01$) only in F group (393.1±62.3pg/mL) and similar among the others (FT: 220.9±21.2pg/mL; CT: 227.3±21.71pg/mL; C: 190.0±24.1pg/mL). NO was higher in CT (728.2±61.5μM) when compared to C (C: 515.1±38.3μM; $P<0.01$) and in FT (770.1±111.2μM) when compared to F (460.6±37.2μM; $P<0.01$). Blood pressure and HR were similar among the groups. Concerning vascular function, the F group (0.24-6±0.1-6M) exhibited increased vasoconstrictory reactivity ($P<0.01$) (i.e. lower concentrations of FNF to promote 50% of the maximum contractile effect) when compared to C (1.3-6±0.2-6M) and FT (0.8-6±0.2-6M). CT (0.69-6±0.1-6M) also needed lower FNF concentration when compared to C. The F group (3.6-6±1.0-6M) also presented an impaired vasodilator response to ACh ($P<0.01$) (i.e. higher concentrations of ACh to promote 50% of the maximum vasodilator effect) compared to C (0.31-6±0.2-6M) and CT (0.32-6±0.1-6M). In addition, FT vasodilatory response (1.1-6±0.5-6M) was similar to C and CT groups.
Conclusions: High fructose intake augmented circulating TG levels and oxidative stress, and impaired vascular reactivity. Exercise training augmented serum NO and reversed the changes caused by chronic ingestion of fructose.

P6301 | BENCH
Simulated hypoxia triggers the release of CD31+/Annexin+ microparticles from endothelial cells in vivo

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Purpose: In our previous studies we have shown that microparticles derived from endothelial cells (EMPs) are released in great numbers into the circulation after myocardial infarction (MI). EMPs are small membrane vesicles and originate from activated, damaged or apoptotic cells. Although the exact mechanism of EMP function still is widely unknown, it has been shown that they modulate inflammation, coagulation and vascular function. In this study we hypothesized that transient hypoxia may act as a trigger for the release of EMPs.
Methods: Fourteen healthy volunteers were subjected to intermittent normobaric hypoxia in an air-conditioned hypoxia chamber simulating an oxygen concentration of a height of up to 5500 meters. Serial venous blood samples were drawn over a period of eight hours. The collected specimens were evaluated for levels of CD31+/Annexin+ and CD31+/Annexin- EMPs using flow cytometry. Significances were calculated using the Wilcoxon matched pairs test, a p-value of <0.05 was considered statistically significant.
Results: During the experiment oxygen concentration was adjusted to a value equivalent to a height of 5500 meters to achieve hypoxic conditions with a peripheral O2 saturation of approximately 78%. Baseline concentrations for CD31+/Annexin+ EMPs were 0.033% (±0.011 SEM). During the first hours of the experiment simulating a height equivalent of 2000 and 4000 meters these levels increased to 0.036% (±0.008 SEM) at 2000 meters and to 0.054% (±0.018 SEM) at 400 meters. After eight hours and a height equivalent of 5500 meters a signif-

icant increase was evident, CD31+/Annexin+ EMP levels were 0.119% (±0.043 SEM, p=0.0188, n=15). No significant differences were found for CD31+/Annexin- EMPs.
Conclusions: These experimental results could provide explanation for the elevated level of EMPs in STEMI patients, showing that temporary hypoxic conditions can trigger the release of the CD31+/Annexin+ EMPs also in healthy volunteers. In our previous studies we have shown that apoptotic bodies can confer pro-survival signals to cardiomyocytes during myocardial ischaemia. Based on the experimental results of this current study we believe that the release of CD31+/Annexin+ EMPs during hypoxia might act as an endogenous survival signal. However, future studies are warranted to further explore this cellular signaling mechanism.

P6302 | BENCH
Exacerbated aging of cerebral arteries is mediated by the adaptor protein p66Shc

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Background: Aging is an independent risk factor for cardiovascular and cerebrovascular disease which, due to the currently aging of western population may soon represent a major healthcare challenge. To date, little is known about the mechanisms of aging of cerebral arteries and whether the aging gene p66Shc is implicated in it. The present study was designed to assess age-induced vascular dysfunction in mice cerebral and systemic arteries in wild type (wt) and p66Shc–/– mice.
Methods: Basilar arteries and size matched second order femoral arteries of 3-months (3M), 6-months (6M) and 2-years old (2Y) mice were studied. Arterial rings, mounted in a myograph for isometric tension recording, were exposed to increasing concentrations of acetylcholine and sodium nitroprusside (SNP). O2- generation was assessed in femoral and basilar arteries using the spin trap 1-hydroxy-3-methoxycarbonyl-2,2,5,5-tetramethyl-pyrrolidine.
Results: Endothelium-dependent, acetylcholine-induced relaxations were assessed in femoral and basilar arteries of 3M, 6M and 2Y of wt and p66Shc–/– mice. In wt mice, endothelial function of the femoral artery was not affected by age unlike in the basilar artery where an age-dependent dysfunction was observed. In p66Shc–/– a similar response was observed in the femoral artery; however, the endothelial dysfunction observed in the basilar artery was blunted as compared to wt. SNP-induced relaxations were comparable in femoral and basilar arteries of 3M, 6M and 2Y wt and p66Shc–/– mice. Electron spin resonance measurement of O2- levels indicated comparable levels of ROS in the femoral arteries of 3M and 2Y of wt and p66Shc–/– mice. Differently, O2- levels in the basilar artery of wt mice were strongly increased by age unlike in p66Shc–/– mice where they remained comparable. Additionally, 2Y but not 3M wt mice presented significant higher levels of O2- compared to p66Shc–/– age-paired mice
Conclusion: Endothelial function of cerebral arteries, but not of size-matched systemic ones is impaired by aging. This process appears to be paralleled by an increased ROS production mediated by the p66Shc–/– gene.

P6303 | BENCH
Lipocalin 2 - a novel factor in ischemic vascular disease

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Introduction: Lipocalin 2 (Lcn-2) is a 25-kDA secreted acute phase protein, which is produced by immune cells, renal tubule cells and a variety of epithelial cancer cells. Recent data suggest that Lcn-2 is up-regulated in acute ischemic kidney injury and promotes tumor progression by induction of angiogenesis. Thus, we hypothesized this protein might be a therapeutic target for the treatment of peripheral arterial disease (PAD).
Methods and results: To test our hypothesis the unilateral mouse hind limb ischemia (HLI) model was conducted. Briefly, limb ischemia was induced by ligation of the femoral artery and blood flow was measured weekly by laser Doppler perfusion imaging. Interestingly, in this animal model knockout of Lcn-2 resulted in an impressive phenotype. Compared to background mice (C57BL/6=wild type=WT) the Lcn-2 –/– mice showed significantly more tissue defects after ligation of the femoral artery. Moreover, the ischemia-associated lesions were more severe as determined by necrosis score (necrosis score Lcn-2 1.8±0.16 vs. WT 0.67±0.19; n=5; $P<0.01$) and amputation rate was higher among the Lcn-2 –/– mice. The decreased expression of mitogen activated protein kinase (MAPK) in ischemic hind limbs of Lcn-2 –/– mice might be responsible for the poor outcome in this animal model. Transplantation of WT-bone marrow to irradiated Lcn-2 –/– mice had no influence on the outcome of the animals suggestinng that observed effects depend more on the endothelium than on inflammatory cells.
To clarify possible effects of Lcn-2 on endothelial cells (EC), in-vitro experiments were performed. Indeed, Lcn-2 induced EC-proliferation as determined by BrdU incorporation (rel. proliferation Lcn-2 10 nM vs. control: 1.4±0.09; n=3; $P<0.001$) and mechanistically these results can be traced back to the induction of the MAPK signaling pathway and phosphorylation of eNOS. Intriguingly, Lcn-2 associated MAPK-activation was blocked by a neutralizing VEGF-antibody suggesting an involvement of this prominent angiogenic factor in Lcn2-induced effects. Real-time PCR analyses showed expression of Lcn-2 and the Lcn-2-receptor by EC as well as a hypoxia dependent up-regulation (rel. Lcn-2 mRNA hypoxia vs. normoxia 1.6±0.2, $P<0.05$; rel. Lcn-2-receptor mRNA hypoxia vs. normoxia 2.62±0.22, $P<0.001$) being a hint for a physiological relevance of this peptide in limb ischemia.
Conclusion: Lcn-2 seems to be an interesting therapeutic target for the treatment of PAD.

P6304 | BENCH
Shock waves induce postnatal vasculogenesis in infarcted myocardium by recruitment of bone marrow derived endothelial progenitors

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Purpose: Recently shock waves at low energy levels were described to induce angiogenesis and regeneration in ischemic tissue. Improvement of myocardial perfusion and relief of angina symptoms in human patients with severe coronary artery disease have been shown. We hypothesized that the recruitment of progenitor cells from bone marrow to infarcted myocardium may be involved as well.
Methods: Sub-lethally irradiated C57Bl/6 wild-type mice received bone marrow transplantation (BmTx) from transgenic GFP mice (C57BL/6Tg (CAG-EGFP) 1Osb/J) (n=6 per group). 4 weeks after BmTx, myocardial infarction was induced by LAD ligation. Treatment group (SWT) received shock wave therapy (0.38mJ/mm^2, 200 impulses, 3Hz) 3 weeks after infarction, whereas control animals (CTR) underwent sham treatment. Hearts were harvested 3 weeks after therapy. GFP positive bone marrow derived cells in the heart were detected by immunofluorescence microscopy. Lectin counterstaining revealed endothelial progenitor cells (EPCs). Gene expression of pivotal factors SDF-1, CXCR4, VEGF receptors and others was performed. Functional outcome was measured with a pressure catheter inserted into the left ventricle. For further mechanistic findings an in-vitro migration assay using human umbilical vein endothelial cells (HUVECs) was performed.
Results: Higher numbers of bone marrow derived endothelial progenitor cells per high power field have been found in the treatment group (CTR 3.98±0.6 vs. SWT 17.89±1.6, $p<0.0001$). The main chemoattractant for EPC recruitment SDF-1 mRNA, was increased (CTR 1.86±0.68 vs. SWT 5.19±1.18, p=0.02). Migration assay revealed higher migration rates (CTR 171.9±15.89 vs. SWT 234.5±25.9, p=0.04). Functional outcome as assessed by pressure catheter showed an increase in dPdtmax (CTR 1957±343 vs. SWT 3007±617.4, $p>0.059$), a decrease in dPdtmin (CTR -1532±251.3 vs. SWT -2603±346.7, p=0.03) and an increase in Tau (CTR 33.68±5.99 vs SWT 124.7±42.15, p=0.09) indicating functional improvement after SWT.
Conclusions: Low energy shock waves induce postnatal vasculogenesis in infarcted myocardium by the recruitment of bone marrow derived endothelial progenitor cells. Shock wave treatment may develop a regenerative adjunct or alternative treatment option to state of the art revascularization in myocardial infarction. Notably, it has already been applied in angina patients without causing any severe side effects.

P6305 | BENCH
Peroxisome proliferator-activated receptor (PPAR)-alpha/gamma agonism enhances arteriogenesis in mice

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Background: Agonism of the peroxisome proliferator-activated receptor (PPAR)-α shows lipid-modifying effects and PPAR-γ agonists enhance insulin-sensitivity. The vascular effects of combined PPAR-α/γ agonism are unknown. The aim of this study was to characterize the impact of the dual PPAR-α/γ agonist aleglitazar on endothelial function, neoangiogenesis and arteriogenesis.
Methods and results: Male C57Bl/6 wild-type (WT, normal chow) and apolipoprotein E-deficient (apoE–/–) mice on Western-type diet were treated with aleglitazar (10 mg/kg i.p.) or vehicle by daily injection.
In-vivo neoangiogenesis was quantitated in WT mice (n=6) by subcutaneously implanting discs covered with cell-impermeable nitrocellulose filters. The vascularized area of the discs was quantified after 14 days by perfusion of the animals with space-filling fluorescent microspheres. Aleglitazar treatment increased neoangiogenesis by 178±18% compared to vehicle ($p<0.05$).
Endothelium-dependent vasorelaxation of aortic rings in response to carbachol was impaired in apoE–/– mice fed with WTD for 6 weeks (relaxation 52±5% of max. contraction; n=6) compared to WT animals (relaxation 18±5% of max. contraction; n=3) ($p<0.001$). Concomitant aleglitazar treatment partially restored endothelial function (relaxation 39±5% of max. contraction; n=6; $p<0.05$).
After hindlimb ischemia induced by right femoral artery ligation (FAL), apoE–/– mice on WTD treated with aleglitazar for 5 weeks before FAL were characterized

by an improvement of endothelial-dependent laser Doppler perfusion (right/left foot ratio 0.40±0.03) 1 week after FAL compared to control animals (right/left foot ratio 0.24±0.01; $p<0.001$). Collateral-dependent perfusion measurements under conditions of maximal vasodilatation 1 week after FAL using fluorescent microspheres demonstrated that compared to WT mice (2 weeks aleglitazar prior to FAL), apoE–/– control mice had an impairment of perfusion restoration (R/L leg ratio in WT 78±13 vs. apoE–/– 56±6; $p<0.001$), which was normalized by aleglitazar treatment (R/L leg ratio 79±5; $p<0.001$).
Molecular analysis showed improved function of endothelial progenitor cells (EPC) with increased expression of phospho-eNOS and phospho-Akt. The effects of aleglitazar on EPC migration and colony forming units were mediated by both PPAR-α and -γ signalling and Akt.
Conclusion: The dual PPAR-α/γ agonist aleglitazar augments neoangiogenesis, endothelial function and arteriogenesis. The study provides evidence for beneficial effects of combined PPAR-α/γ agonism on vascular function mediated by or in addition to its metabolic actions.

ATHEROSCLEROSIS AND INFLAMMATION

P6307 | BENCH
oxLDL decreases wnt1 which promotes CD36 through b-catenin and PPAR-r signaling pathway in macrophage

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Aims: Many present researches show wnt signaling plays important role in the initiation of atherosclerosis. Wnt1 participates in the migration of macrophages. our group want to further investigate the role of wnt1 in the formation of macrophage foam cell which promotes atherosclerosis, so we study the relationship between wnt1 and scavenger receptors in macrophages.
Methods and results: First we found that oxLDL suppress the expression of wnt1 in THP-1 cells, then THP-1 cells were treated with siRNA or overexpression plasid of wnt1, CD36 was decreased or increased respectively. We also got the similar results in GM-CSF stimulated human perpheral blood monocytes. We then used inhibitors of β-catenin, protein kinase C (PKC) and PPAR-γto demonstrate wnt1 regulates the expression of CD36 through β-catenin pathway and PKC-PPAR-γ signaling, furthermore co-immunoprecipitation was used to find β-catenin pathway is dependent on PPAR-γ. Existing researches show oxLDL activates CD36 through PKC-PPAR-γpathway. Meanwhile, we also found oxLDL can regulates CD36 production through ERK-β-catenin signaling.

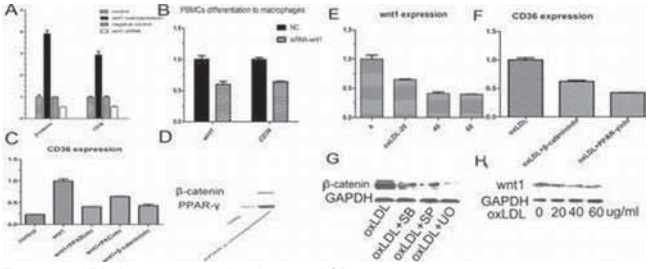

Figure 1. oxLDL decreases wnt1 then increased CD36.

Conclusions: In the differentiation process from PBMCs to macrophages, oxLDL inhibit the expression of wnt1 but induce the CD36 production by activation of both β-catenin and PPAR-γ. Wnt1 induces the expression of CD36 through β-catenin pathway and protein kinase C-PPAR-γ signaling. This vicious circle promotes macrophage foam cell formation which contributes atherosclerosis ultimately.

P6308 | BENCH
Combined administration of eicosapentaenoic acid and docosahexaenoic acid reduces atherosclerotic lesion in apolipoprotein E-deficient mice

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Background: Recent studies demonstrated that macrophages play an important role in the progression of atherosclerosis by promoting inflammatory responses. We have reported that highly purified eicosapentaenoic acid (EPA) reduces and stabilizes atherosclerotic lesions in apolipoprotein E-deficient (ApoE-deficient) mice by inhibiting activation of macrophages. However, effects of docosahexaenoic acid (DHA), one of the major n-3 PUFAs, on the development of atherosclerosis is still under debate. In this study, we examined whether additional dosage of DHA to EPA presents more effective anti-atherosclerotic properties in ApoE-deficient mice.
Method and result: Eight-week-old ApoE-deficient mice were fed on western-type diet supplemented with 2.5% (w/w) EPA, 5% (w/w) omega-3-acid ethyl esters which includes 2.3% (w/w) EPA and 1.9% (w/w) DHA (EPA + DHA), or none of n-3 PUFAs (control group) for 20 weeks. There were no significant differences in blood pressure and the levels of total cholesterol and free fatty acid in these groups. In EPA group, the level of triglyceride was significantly higher than control group. En face Sudan IV staining of the aorta revealed that EPA or EPA+DHA treatment significantly attenuated atherosclerotic lesion progression compared with control group, and the effect was enhanced in EPA+DHA group (control vs. EPA vs. EPA+DHA; 17.0±6.7 vs. 12.0±6.5 vs. 5.9±4.8%, $P<0.01$). Result of histological analyses demonstrated that EPA+DHA treatment significantly decreased lipid deposition (7.8±2.7 vs. 13.5±2.7%) and matrix metallopeptidase-9 (MMP-9) expression (2.7±1.6 vs. 7.5±2.7%) in atherosclerotic lesions in aortic sinus compared with control group ($P<0.05$ and $P<0.01$, respectively). EPA+DHA treatment also decreased the expression of F4/80, a marker of macrophage, in abdominal aorta compared with control group ($p<0.01$). In vitro experiment using RAW264.7, a murine macrophage cell line, demonstrated that pretreatment with EPA or DHA attenuated the up-regulation of MMP-9 and MCP-1 induced by LPS.
Conclusion: Combined administration of EPA and DHA showed better anti-atherosclerotic effect compared with EPA treatment in ApoE-deficient mice. Combination therapy of n-3 PUFAs may provide a new therapeutic option.

P6309 | BENCH
A newly developed apoA-I mimetic peptide with a D-amino acid promotes HDL via ABCA1-mediated cholesterol efflux

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Apolipoprotein (apo)-AI stimulates cholesterol efflux via the ATP-binding cassette transporter A1 (ABCA1), which generates HDL and reverses the macrophage foam-cell phenotype. Despite these anti-atherogenic roles, the impact of specifically promoting ABCA1 cholesterol efflux on atherosclerosis development is not well understood. We previously developed an apoA-I mimetic peptide, FAMP (Fukuoka University ApoA-I Mimetic Peptide – type 5; ALE HLF TLY EKA LKA LED LLK KLL) which had ABCA1-mediated pathway. Therefore, a novel synthetic apoA-I mimetic peptide with a D-amino acid was newly developed (FAMP-D1). The FAMP-D1 was added d-alanine at its C-terminus end to the FAMP consists of 25 amino acids (ALE HLF TLY EKA LKA LED LLK KLL d-A). Serum apoA-I from human plasma and FAMP-D1 could take-up cholesterol. After stimulation with LXR/RXR-agonists, FAMP-D1-mediated cholesterol efflux were increased, as well as with serum apoA-I, in addition specific cholesterol efflux with FAMP-D1 was much higher than those with FAMP and apoA-I (13.6% increasing of FAMP, 57.1% increasing of serum apoA-I, $P<0.01$). Furthermore, after incubation of FAMP-D1 with human serum, FAMP-D1 was significantly elevated the efflux capacity of HDL. In conclusion, a newly developed apoA-I mimetic peptide with a D-amino acid remarkably removes cholesterol and forms HDL via an ABCA1 specific pathway.

P6310 | BENCH
Chlamydia pneumoniae infection promotes vascular endothelial cell migration and angiogenesis through IQGAP1 related signaling pathway

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Purposes: Pathological angiogenesis is associated with unstable vulnerable atherosclerotic plaques and contribute to plaque rupture. Vascular endothelial cell (VEC) migration is a key step in angiogenesis. Multiple reports have demonstrated an association between Chlamydia pneumoniae infection and plaque vulnerability. However, how C. pneumoniae infection can result in plaque instability remains unclear. C. pneumoniae infection has been shown to promote cell migration. Whether C. pneumoniae infection might cause plaque destabilization through enhancing VEC migration and angiogenesis is unknown. IQGAP1 has been implicated as a regulator of cell motility and angiogenesis. In this study, we attempt to observe the effects of C. pneumoniae infection on VEC migration and angiogenesis, to investigate the role of IQGAP1 related signaling pathway in this process.
Methods and results: VEC migration by wound healing assay and tube formation by tube formation assay were both significantly enhanced after C. pneumoniae infection compared to the control group ($P<0.05$). Co-immunoprecipitation (Co-IP) results revealed that C. pneumoniae infection of VECs significantly stimulated IQGAP1 phosphorylation. Then, we found C. pneumoniae infection significantly increased Src activity rather than PKC activity, and PP2, a selective Src tyrosine kinase inhibitor, but not the PKC inhibitor chelerythrine or GF 109203X, markedly decreased the level of IQGAP1 phosphorylation stimulated by C. pneumoniae infection, and suppressed the infection-induced VEC migration and tube formation ($P<0.05$). Moreover, C. pneumoniae infection also induced recruitment of IQGAP1 to lamellipodia required for cell migration and angiogenesis. These data imply that IQGAP1 phosphorylation mediated by Src but not PKC plays an important role in C. pneumoniae infection-induced VEC migration and angiogenesis. In addition, the infection-induced VEC migration and tube formation were also inhibited by wiskostatin, an N-WASP inhibitor ($P<0.05$), and N-WASP was found to be recruited to lamellipodia after the infection, suggesting a possible role of N-

WASP in VEC migration and angiogenesis caused by the infection. Furthermore, knockdown of IQGAP1 by siRNA was found to inhibit both the infection-induced N-WASP phosphorylation and the recruitment of N-WASP to lamellipodia. Co-IP analysis also revealed that IQGAP1 physically associates with N-WASP in the infected cells. The results suggest a link between IQGAP1 and N-WASP.
Conclusion: C. pneumoniae infection promotes VEC migration and angiogenesis possibly through IQGAP1-N-WASP signaling pathway.

P6311 | BENCH
Repetitive treatment of percutaneous carbon dioxide mist prevents high fat diet-induced arteriosclerosis in extremely small size minipig

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Background: Carbon dioxide (CO2) baths have been used to treat a variety of diseases. We have reported that treatment with a few micrometers of CO2 particles atomized by double-fluid nozzles (CO2 mist) could improve left ventricular ejection fraction in a rat myocardial infarction model. Here, we investigated whether CO2 mist therapy could prevent a noninvasive high fat and high cholesterol diet (HFCD)-induced atherosclerosis and endothelial dysfunction in extremely small size minipigs, Microminipigs (MMPs), which have a potency to be a suitable animal model for human atherosclerosis.
Methods: Male MMPs, weighing approximately 6 kg were used. Atherosclerosis model was produced by feeding HFCD for 8 weeks. Using the device equipped with double-fluid nozzles, CO2 gas and water compounded and compressed at 4 barometric pressures. Without anesthesia, lower bodies of MMPs were wrapped in a polyethylene bag filled with CO2 mist by this gas mist generator. CO2 mist was treated to MMPs for 30 minutes twice a day. Serum total cholesterol (T-cho) and low-density lipoprotein (LDL) levels were measured every 2 weeks. After 8 weeks, coronary artery was carefully extracted and vascular relaxation response was measured. Furthermore, gene expression of G protein-coupled receptor 120 (GPR120), which regulates adipogenic processes, in pericoronary arterial adipose tissue was measured.
Results: HFCD significantly increased serum T-cho and LDL levels at 2 weeks and later. At 8 weeks, serum T-cho and LDL levels were 346±4 and 258±8 mg/dL, respectively. These levels in the normal diet group were 131±9 and 69±10 mg/dL, respectively. Treatment of CO2 mist slightly depressed these lipid levels (T-cho, 334±17; LDL, 235±19 mg/dL). HFCD reduced endothelium-dependent relaxation of coronary artery to bradykinin at 8 weeks. Despite similar body weight, blood pressure and serum lipid levels, treatment of CO2 mist significantly improved the endothelium-dependent relaxation response reduced by HFCD. On the other hand, smooth muscle-dependent relaxation of coronary artery to nitroprusside was similar among the groups. GPR120 expression in pericoronary arterial adipose tissue was significantly decreased by HFCD, and treatment of CO2 mist recovered the expression.
Conclusion: Repetitive treatment of percutaneous CO2 mist may be potentially useful for preventing arteriosclerosis. Beneficial effects of CO2 mist may be partially mediated via upregulation of GPR120 in perivascular adipose tissue.

P6312 | BENCH
Complex of oleacein with hemoglobin and haptoglobin may protect atherosclerotic plaques against destabilization

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Purpose: A prospective study (EPIC-Spain, 2012) demonstrated unequivocally that the high consumption of olive oil is a factor reducing cardiovascular mortality. This effect may be associated with anti-oxidative and anti-inflammatory activity of oleacein – a secoiridoid present in extra virgin olive oil. Since oleacein aglycones strongly interact with red blood cell membranes, they can also be present in atherosclerotic plaque during hemorrhage.
The aim of the study was to establish the role of oleacein in regulation of inflammatory responses of plaque macrophages.
Methods: Human carotid atherosclerotic plaques (n=20) were isolated from arteries during endarterectomy. Human periphery blood monocyte-derived macrophages were isolated from young healthy volunteers. MMP-9, TF and IL-10 level was measured using ELISA tests, CD163 and IL-10 expression was measured using FACS method.
Results: Incubation of plaques with oleacein in concentration range of 10 to 20μM significantly decreased secretion of MMP-9 and TF (following stimulation with LPS 1 ng/ml) as compare to matching control. Increased IL-10 production observed at the same time suggested the conversion of the phenotype of plaque macrophages from pro-inflammatory M1 to anti-inflammatory M2C. In fact, we demonstrated that the stimulation of human of macrophages in the presence of a complex of oleacein with hemoglobin and haptoglobin 1-1 as well as 2-2 resulted in a significant increased expression of CD163 receptor and IL-10. Such properties have not been demonstrated for other polyphenols, i.e. oleuropein and tyrosol.
Conclusion: In conlusion, oleacein is the main protective factor of extra virgin olive oil with respect to prevention of acute coronary syndromes.

P6313 | BENCH
Molecular determinant of the development of acute aortic dissection

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Acute aortic dissection (AAD) is a common disease with sudden onset and high mortality, caused by the disruption of the intimomedial layer followed by the longitudinal tearing of the aortic walls. Currently, effective medical therapy for AAD is not available because molecular pathogenesis of AAD is largely unknown.
Hemodynamic stress and aortic wall stiffening are known risk factors for AAD. To better understand the stress response to these risk factors, we created a mouse model of aortic stiffening by periaortic CaCl2 treatment and hemodynamic stress by angiotensin II infusion (Ca+AngII). We first examined the aorta of wild type mice (WT) after Ca+AngII. Approximately 40% of mice showed microscopic medial injuries in the suprarenal aorta 1 week after the Ca+AngII treatment, which healed with fibrosis in 6 weeks. Histological analysis showed infiltration of macrophages with STAT3 activation at the site of the microscopic injuries. We investigated the significance of STAT3 activation in macrophages by using macrophage-specific knockout of SOCS3, a negative regulator of STAT3 signaling (mSOCS3-KO). Both WT and mSOCS3-KO showed equivalent extent of microscopic injuries in aorta with 40% of frequencies 1 week after Ca+AngII, indicating that macrophage STAT3 pathway does not play a major role up to this stage. However, 25% mSOCS3-KO developed AAD in the suprarenal aorta 6 weeks after Ca+AngII, while only 9% of WT showed such a phenotype. Histological analysis showed the disruption of the intimomedial layer, intramural hematoma and the double-barrel appearance of true and false lumens, hallmarks of AAD, in the enlarged aorta. Stage-specific transcriptome analysis showed the enhanced expression of cell cycle genes in stressed aorta, followed by the activation of inflammatory genes at the stage of microscopic injury in mSOCS3-KO compared to WT before the development of AAD. The activation of cell cycle was confirmed by the histological analysis that showed Ki67 staining in the inflammatory cells in the suprarenal aortic walls. Flow cytometric analysis revealed the proinflammatory M1-skewed differentiation of mSOCS3-KO macrophages compared to WT in the aorta with microscopic injury by Ca+AngII treatment.
These results suggest that activation of macrophage STAT3 signaling resulted in the expansion and M1 polarization of macrophages at the stage of microscopic injury preceding the development of AAD. Deciphering such sequential molecular events during the development of AAD will be essential to develop a new diagnostic and therapeutic strategies for this lethal disease.

P6314 | BENCH
Macrophage-derived exosomes damage endothelial cells in experimental hypertensive models

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Background: Hypertension is one of the most important risk factors of cardiovascular diseases. Sustained hypertension induces chronic inflammation, which causes cardiac remodeling and dysfunction although it is a protective response for persistent stresses. However, it is fully unknown that the role of the inflammatory cells such as macrophages on cardiovascular diseases which infiltrate a damaged cardiovascular tissues. It has been recently suggested that exosomes contribute to intracellular communication through the proteins and microRNAs and proteins from excretory cells. Here, we investigated the effects of exosomes secreted from macrophages in experimental hypertensive models.
Design and methods: (1) Hypertensive model rats were made by continuous infusion of angiotensin II (Ang II, 200 μg/kg/min) or a nitric oxide synthase inhibitor (Nω-nitro-L-arginine methyl ester; L-NAME, 1 mg/mL in drinking water) for 7 days. Exosomes from serum were purified by ultracentrifugation. Human coronary arterial endothelial cells (HCAECs) were treated with serum exosomes. (2) Human THP-1-derived macrophages were stimulated by Ang II (100 nM) or hypoxia, and exsosomes in culture media were purified. HCAECs were treated with medium exsosomes. (3) Proteomic analysis of THP-1-derived exosomes was performed.
Results: (1) Elevated blood pressure and left ventricular hypertrophy were observed by Ang II and L-NAME administration. An amount of proteins in exosomes was increased in both hypertensive rats compared with that in normotensive rats. Addition of serum exosomes from hypertensive rats activated some signal transduction pathways such as c-Jun N-terminal kinase, p38 mitogen-activated protein kinase, and Akt in HCAECs. The proteins in HCAECs were positive for CD68 antibody which is a specific marker of macrophages. (2) Activated macrophages increased an amount of exsosomal proteins and changed the constitutive proteins in medium exosomes. Medium exosomes collected in Ang II- and hypoxia-stimulated macrophages activated the same signal transduction pathways as the serum exosomes. These stimulations increased intercellular adhesion molecule-1 in HCAECs, suggesting that stimulated THP-1-derived exosomes may induce proinflammatory effects and damage the endothelial cells. (3) Proteomic analysis revealed that there were different protein profiles in THP-1-derived exosomes among non-stimulation, and the stimulation of Ang II and hypoxia.
Conclusions: Endothelial damage by hypertension may be partially associated with activated macrophages-derived exosomes.

P6315 | BENCH
Inhibition of DPP-4 attenuates monocyte inflammatory response through suppression of MAPK phosphorylation and ameliorates the development of CaCl2-induced abdominal aortic aneurysm in mice

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Purpose: Abdominal aortic aneurysm (AAA) is characterized by the destruction of tissue architecture due to chronic inflammation of unknown etiology. Recent studies showed that a dipeptidyl peptidase-4 (DPP4) inhibitor directly inhibites smooth muscle cell proliferation and monocyte inflammation independent of the increase in circulating glucagon-like peptide-1 level. We investigated the potential effect of a DPP4 inhibitor, vildagliptin, on the formation of abdominal aortic aneurysm (AAA) in mice.
Methods: For induction of AAA, we applied 0.5 M CaCl2 to the infrarenal aorta, then mice received vildagliptin (30mg/kg/day, n=10) or a vehicle (n=10) with oral administration for six weeks. Saline-treated mice were served as controls (n=10). Incidence of AAA was defined as external diameter >1.5 fold of the average of the control group. The expressions of mRNA were analyzed by real-time quantitative PCR using aortic tissue after one week CaCl2 treatment. The effects of vildagliptin were investigated in a monocyte cell line, RAW 264.7 cells.
Results: The expression of DPP-4 in abdominal aorta was strikingly increased at 6 weeks after application of CaCl2. Then, vildagliptin significantly attenuated AAA formation (external diameters; 1.11±0.06 mm [CaCl2] vs. 0.95±0.05 mm [CaCl2+vildagliptin] vs. 0.64±0.02 mm [Saline], $p<0.05$, respectively, n=10). Histological analysis showed that the recruitment of macrophages into AAA lesion in CaCl2 group was significantly greater than that in vildagliptin group (3.3±2.0 cell/μm^2 vs. 1.2±2.2 cell/μm^2, $p<0.05$). Quantitative PCR demonstrated that the elevated expressions of MMP -2, -9, -12 and monocyte chemotactic protein-1 in vehicle group at one week after CaCl2 treatment were significantly decreased in the vildagliptin group. In addition, mRNA expression of Hspa5 as a marker of Endoplasmic reticulum (ER) stress and p47phox as a marker of oxidative stress were also reduced in the vildagliptin group. In vitro experiments, induction of interleukin-6 from RAW cells in response to lipopolysaccharide was directory suppressed by vildagliptin alone (20nM-2μM), accompanied by suppression of MAPK phosphorylation (JNK and ERK) and NF-κB activation.
Conclusion: Vildagliptin attenuated the development of CaCl2-induced AAA in mice. Anti-inflammatory effects through suppressing MAPK activation in macrophages may contribute to the protection of AAA.

ENDOTHELIAL FUNCTION: CLINICAL

P6317 | BEDSIDE
Changes in shear stress are major determinants of flow-mediated dilation and constriction: two complementary markers of endothelial function

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Introduction: Mediated dilation (FMD) measures the endothelium-dependent vasodilator response to a short-term increase in local shear stress. Complementary to this, low-flow mediated vasoconstriction (L-FMC) measures vasoconstrictor responses in response to a decrease in local shear stress. Like FMD, L-FMC is mediated by endothelial autacoids, and it is abrogated by removal of the endothelium. No study has tested as yet whether a relationship exists between decrease in blood flow/shear stress and the corresponding L-FMC.
Materials and methods: We evaluated radial artery FMD and L-FMC along with the changes in blood flow and shear rate/stress in 586 participants (79.6% men, mean age 67±13 years) using high-resolution ultrasound and Doppler. In models adjusted by age, sex and presence of cardiovascular disease, baseline and hyperemic shear stress were related to radial artery FMD and L-FMC. Stepwise multiple analyses examining clinical correlates of endothelial function parameters showed that age, sex and a history of hypertension are related to L-FMC ($R2=0.07$; $P<0.001$). Similarly, FMD was associated with age and sex ($R2=0.07$; $P<0.001$). When resting shear rate was incorporated, this association was strengthened for both L-FMC and FMD (respectively, R2=0.14 and R2=0.07). Similar results were obtained when the corresponding changes in shear rate were considered (R2=0.14 for L-FMC and R2=0.07 for FMD), but the relationships between risk factors and L-FMC and FMD were attenuated.
Discussion: Like for FMD, we show that changes in blood flow/shear stress are major correlates of L-FMC. These observations support the concept that FMD and L-FMC measure two complemetary aspects of endothelium-dependent, shear-induced, vasomotion.

P6318 | BEDSIDE
Allopurinol and endothelial function

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Background: Uric acid levels are associated with endothelial dysfunction (ED) and atherosclerosis. Xanthine oxidase inhibition with allopurinol decreases uric acid levels and oxidative stress and improves endothelial function.
Purpose: This study investigated the effect of high-dose allopurinol therapy on endothelial function in hyperuricemic asymptomatic patients without any overt cardiovascular disease.
Methods: 60 subjects with uric acid (UA) ≥5 mg/dl, all non-smokers without any known cardiovascular disease were studied. They were divided in two groups. Both treatment and placebo groups consisted of 30 patients. In the treatment group, daily oral 600 mg allopurinol was started after randomization and maintained for 12 weeks. Endothelium-dependent dilation was assessed by measuring flow mediated dilation (FMD) of the brachial artery and endothelium independent dilation was assessed by measuring changes in brachial artery diameter in response to sublingual nitrate administration (NMD). UA, FMD and NMD were measured at baseline and at the end of the therapy.
Results: At baseline there were no significant differences between groups regarding: age, blood pressure, body mass index, glucose, lipids and UA levels, FMD and NMD. FMD improved significantly after treatment in the allopurinol group 8, 2±1, 31% vs. 6, 92±0, 95% (p=0, 01). UA was significantly lower after treatment in the allopurinol group 5, 63±0, 71 vs. 7, 19±0, 87 mg/dl (p=0, 0003). NMD did not change significantly in the allopurinol group, 10, 66±0, 59% vs. 10, 79±1, 01% (p=0, 72). There were no significant differences regarding UA levels in the placebo group after and before the treatment 7,35±0,76 mg/dl vs. 7,27±0,85 mg/dl (p=0,82). FMD did not change significantly in the placebo group 6, 99±0, 81% vs. 6, 88±1, 01% (p=0, 7). NMD did not change significantly in the placebo group 10, 38±0, 63% vs. 10, 48±0, 99% (p=0, 79). No significant correlation was found (r=0, 15, p=0, 56) between the variation of UA plasma levels (UA after treatment - UA at baseline) and the variation of FMD (FMD after treatment - FMD at baseline) in the allopurinol group.
Conclusions: These results suggest that allopurinol improves endothelium-dependent dilation, but the improvement was not correlated with uric acid levels. The mechanism of improvement is correlated with its ability to reduce vascular oxidative stress.

P6319 | BEDSIDE
Warfarin administration is associated with an increase of vascular calcification biomarker,RANKL

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Purpose: Over the past three decades, the utility of oral anticoagulation with warfarin in thromboembolic disease has been fully demonstrated. Although vitamin K deficiency can induce osteoporosis, patients who are taking warfarin must be prohibited their intake of vitamin K-rich foods, like as green vegetables and "natto", a popular Japanese soybean food fermented with Bacillus subtilis, which continues to synthesize vitamin K in the intestine. Vitamin K-dependent matrix Gla protein has been known as a potent inhibitor of the arterial calcification. We hypothesized that warfarin therapy affects both bone mineral metabolism and vascular calcification.
Methods: We prospectively included 40 consecutive atrial fibrillation (AF) patients high risk for arteriosclerosis (age 68±6 y; 6 female). Exclusion criteria include the following: the CHADS2 scores >4, age >80 years old, HbA1c>8.0%, BP>160/100 mmHg. Twenty-two patients had been treated with warfarin at least 12 months (WF group), or 18 patients without warfarin (non-WF group). Bone alkaline phosphatase (BAP) and under carboxylated osteocalcin (ucOC) and receptor activator of nuclear factor-kappaB ligand (RANKL) were measured as bone metabolism markers, reactive hyperemia index (RHI) measured by Endo-PAT2000 was used as an indicator of vascular function, were performed in patients with AF treated with warfarin or the new anticoagulants (NOAC).
Results: In WF group, serum levels of ucOC were significantly higher than those in non-WF group (10.3±0.82 vs. 3.4±0.91 ng/mL; $P<0.01$), similarly, serum levels of RANKL in WF group were higher than those of the other (0.60±0.055 vs. 0.37±0.054 ng/mL; P=0.007), suggesting WF group were more preventing bone mineral metabolism than non-WF group. Moreover RHI was significantly lower in WF group compared to those in non-WF group (1.48±0.11 vs. 1.88±0.12; P=0.017). There were no significant differences in patients' background characteristics including smoking, PWV, DXA scan score, and other clinical indicators between the two groups. These data suggest that long-term warfarin therapy may be associated with serious bone mineral loss and increased vascular calcification.
Conclusion: Warfarin therapy may be associated with vascular dysfunction and bone mineral loss.

P6320 | BEDSIDE
Vascular function and ocular involvement in sarcoidosis

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Purpose: Sarcoidosis (Sar) is a multisystemic inflammatory disease. It has been

shown that Sar patients have impaired endothelial function, augmented arterial stiffness and increased inflammatory status. Ocular involvement occurs in 15-25% of Sar patients mainly in the form of uveitis. The study was designed to determine if uveitis as a manifestation of ocular Sarcoidosis is associated with an extensive vascular dysfunction, as a result of a stronger inflammatory process.
Methods: We enrolled 62 Sar patients and 62, age and sex matched, control subjects (CI). Sar patients were divided in those with ocular Sarcoidosis (OS) (23 patients) and in those without ocular Sarcoidosis (WOS) (39 patients). Endothelial function was evaluated by flow-mediated dilatation (FMD). Carotid-femoral pulse wave velocity (PWV) was measured as an index of aortic stiffness and augmentation index (AIx) as a measure of arterial wave reflections.
Results: Although there was no significant difference in sex, age and mean arterial pressure, patients with OS compared to WOS patients and CI subjects had impaired FMD (4.48±2.38% vs. 6.46±1.92% vs. 8.30±3.47%, $p<0.001$), increased AIx (25.00±8.79% vs. 17.99±10.99% vs. 13.76±10.76%, p=0.001) and increased PWV (8.48±2.25 m/sec vs. 7.00±1.12m/sec vs. 6.85±1.51 m/sec, $p<0.001$). Logistic regression analysis, after adjustment for possible covariates (such as age, sex, smoking habits, the presence of arterial hypertension, diabetes mellitus, dyslipidemia and the treatment with cortisone), revealed that impaired FMD in Sar patients was independently associated with increased Odds of ocular involvement [Odds ratio=0.64, 95%CI (0.43, 0.95), p=0.03]. More precisely ROC curve analysis revealed that FMD had a significant diagnostic ability for the detection of OS (AUC=0.73, p=0.002) and a FMD value below 4.95% has a modest sensitivity (61%) and a significant specificity (80%).
Conclusion: In the present study we have shown that Sar patients with ocular sarcoidosis have impaired endothelial function and increased arterial stiffness compared to Sar patients without ocular involvement. These results strengthens the vascular theory considers uveitis a consequence of vascular dysfunction in Sar patients.

P6321 | BEDSIDE
CD-144 positive endothelial microparticles are increased in patients with systemic inflammatory response syndrome after TAVI

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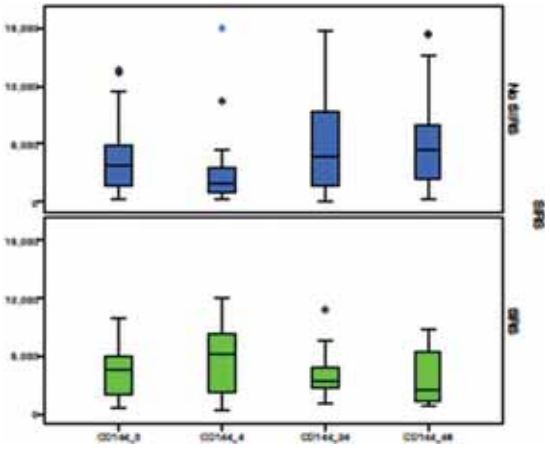
Background: The development of a systemic inflammatory response syndrome (SIRS) after TAVI is associated with peri-procedural complications such as major bleedings and vascular complications.
Microparticles are proinflammatory, procoagulant membrane vesicles released from various cell types and may have a key role in the endothelial and hemostatic response to SIRS. We assessed the association of CD144 positive endothelial microparticles (EMP) with the development of SIRS in patients undergoing TAVI.
Methods and results: We measured EMP, white blood cell count, interleukin 6 (IL-6), IL-8, and procalcitonin (PCT) before and serially at 4h, 24h, and 48h after transfemoral TAVI in 51 consecutive patients (57% male, age 81.4±6.5 years, left-ventricular ejection fraction 50.4±12.7%; logistic EuroSCORE 27.0±16.6). The occurrence of SIRS was defined as fulfilling two of the following criteria during the first 48 h: fever, tachycardia, hyperventilation, and leucocyte count >12 or <4 (10^9/L).
CD144 positive EMP level at baseline was 3152.8 (1305.7 to 5064.2) per μL. Patients with uneventful course showed a significant EMP decline at 4h after the procedure (from 3152.8 to 1553.0; p=0.02).
11 of 51 patients developed a systemic inflammatory response syndrome after TAVI. In these patients, the EMP level at 4h after the procedure was significantly higher in SIRS patients (5224.9 vs. 1553.0 per μL; p=0.02) than in patients with uneventful course. Furthermore, the development of SIRS was associated with an elevation of IL-6 ($p<0.001$) and IL-8 (p=0.001) and a leucocyte increase (p=0.008) but not detectable by PCT elevation (p=0.11) during the first 4 hours.



EMP & development of SIRS after TAVI.

Conclusions: TAVI patients developing SIRS showed higher EMP levels directly after the procedure than patients without complications.

P6322 | BEDSIDE
The impact 25-hydroxyvitamin D3 and D2 serum levels on vascular function in patients with coronary artery disease

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Purpose: Vitamin D deficiency is highly prevalent worldwide and is associated with the presence of coronary artery disease (CAD). There are two major forms, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Endothelial function and arterial stiffness are key players in the pathophysiology of atherosclerotic disease. We study the effect of the different vitamin D fractions (D3/D2) on arterial wall properties in CAD patients.
Methods: We included 252 (mean aged 62±11 years) patients with stable CAD, one month after percutaneous coronary intervention. Endothelial function was evaluated by flow mediated dilation (FMD). Carotid femoral pulse wave velocity (PWV) was measured as an index of arterial stiffness and augmentation index (AI) as a measure of reflected waves. Measures for 25(OH)D2 and 25(OH)D3 were performed using Liquid Chromatography Mass Spectrometry technology. Subjects with vitamin D levels below 20, between 20 to 30 and above 30ng/ml were characterized as having deficiency, insufficiency and sufficiency respectively.
Results: From the study population, 155 (62%), 66 (26%) and 31 (12%) were categorized as having vitamin D deficiency, insufficiency and sufficiency respectively. Subjects with vitamin D deficiency and/or insufficiency had significantly higher D2 to D ratio compared to subjects with vitamin D sufficiency [0.029 (0.007-0.039) vs. 0.013 (0.012-0.021) vs. 0.009 (0.008-0.012), $p<0.001$]. There was no difference between subjects with vitamin D deficiency, insufficiency and sufficiency in FMD (5.03±2.09% vs. 4.52±2.06% vs. 4.80±2.05%, p=0.31), AI (23.68±8.42% vs. 24.14±9.00% vs. 22.52±11.31%, p=0.71) and PWV (8.94±2.05m/sec vs. 9.26±2.64m/sec vs. 8.42±1.85m/sec, p=0.23). Interestingly, FMD was positively associated with D2 to D ratio (rho=0.13, p=0.02) and subjects with D2 levels <0.3ng/ml had impaired FMD compared to those with increased D2 levels (p=0.048).
Conclusion: Vitamin D insufficiency/deficiency is highly prevalent in CAD subjects. Although vitamin D status is not associated with arterial stiffness and endothelial function, D2 concentrations are positively associated with endothelial function. These findings may suggest a beneficial role of vitamin D2 levels in vascular health.

P6323 | BEDSIDE
Depletion of Uric Acid due to URAT-1 loss-of-function mutation causes endothelial dysfunction in hypouricemic patients

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Introduction: Uric acid (UA) has been reported to provide an antioxidant defense and preserves endothelial function. This suggests that the low level of serum UA (SUA), hypouricemia, might cause endothelial dysfunction. Uric acid transporter (URAT) 1 is expressed in the kidney and vessels and is the major determinant of SUA. The loss-of- function mutations of URAT1 cause renal hypouricemia with high urinary excretion of UA (FEUA), which is often associated with acute renal failure.
Purpose: We examined whether a decrease of SUA associated with endothelial function in patients with hypouricemia carrying URAT1 mutations.
Method: Clinical study: 26 patients with hypouricemia and 8 control subjects were involved. Genetic analysis revealed URAT1 gene mutations in hypouricemia. Endothelial function was evaluated using flow mediated dilation (FMD). Experimental study: mRNA of uric acid transporters extracted from vessels were determined by RT-PCR.
Result: Mean SUA was decreased and FEUA was increased in hypouricemia compared to control (SUA; hypouricemia 1.14 mg/dL vs. control 4.49 mg/dL, $P<0.001$, FEUA; hypouricemia 40.29% vs. control 9.17%, $P<0.001$). There was no differences in FMD between 2groups (FMD; hypouricemia 5.56% vs. control 5.63%, P=0.961), while there was a positive correlation between FMD and SUA (R=0.445, P=0.026) in hypouricemia. URAT1 loss-of-function mutations (G77A, G269A, C445T, G446A, G774A, C1137, A1145T and T1253G) were found in 21patients with hypouricemia, but not in 5 patients, 6 were homozygous, 8 were compound heterozygous, and 7 were heterozygous. In hypouricemia, SUA in homozygous (0.70mg/dL) and compound heterozygous (0.68mg/dL) were lower with higher EFUA than those with other groups, and SUA of heterozygous (1.57mg/dL) and no mutation (1.80mg/dL) were lower than that of control, suggesting the impact of allele-dependent effects on UA metabolism. The FMD was significantly impaired in homozygous (2.73%) than those with the heterozygous (8.23%), no mutation (6.99%) and control. The FMD with compound heterozygous (4.44%), tend to be lower than heterozygous and no mutation. Most of homozygote mutation harbored G774A, involving the impact of mutation G774A on FMD. There was difference in FMD between 2 groups (G774A homogenous

2.73% vs. G774A heterozygote 5.93%, P<0.05) independent of SUA, although vessels expressed mRNA of uric acid transporters (URATv1, ABCG2, MRP4 and MCT9) except of URAT1. Allopurinol or vitamin C improved FMD in hypouricemia.
Conclusion: Depletion of uric acid due to URAT-1 loss-of-function mutation causes endothelial dysfunction in hypouricemic patients.

P6324 | BEDSIDE
Effects of atorvastatin treatment on endothelial function and inflammatory status of ischemic heart failure patients: The impact of renal function

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Purpose: Ischemic heart failure (HF) is characterized by increased inflammatory status and impaired endothelial function which further deteriorates exercise tolerance and outcomes. Impaired renal function is a major determinant of adverse prognosis in HF. Statins, beyond their lipid lowering role, exert beneficial effect on endothelial function in patients with atherosclerosis. Aim of the present study was to examine the impact of atorvastatin treatment and renal function on endothelial function and biomarkers of inflammation and cardiac remodelling in HF patients.
Methods: We studied the effect of 4 weeks administration of atorvastatin in 23 patients with ischemic HF. The study was carried out on two separate arms, one with atorvastatin 40mg/d and one with atorvastatin 10mg/d (randomized, double-blind, cross-over design). Endothelial function was evaluated by flow-mediated dilation (FMD) of the brachial artery. Creatinine clearance was estimated based on MDRD formula. Serum levels of tumor necrosis factor alpha (TNFa), of brain natriuretic peptide (BNP) and of matrix metalloproteinase-9 (MMP9) levels were measured by ELISA as indices of inflammatory status, left ventricle loading conditions and remodeling respectively. Total cholesterol (TC) was measured based on common biochemistry techniques.
Results: Compared to baseline, treatment with 40 mg/d of atorvastatin improved FMD (3.16±2.98% vs. 6.05±2.45%, p=0.001), TNFa (p=0.01) and MMP9 levels (p=0.04) while there was no impact in BNP levels (p=0.66]. Moreover, compared to baseline, treatment with atorvastatin 10mg/d also improved FMD (3.24±3.12% vs. 4.20±2.09%, p=0.08) and TNFa (p=0.01) but had no impact on MPP9 (p=0.76) and BNP levels (p=0.40). The increase in FMD was greater with the dose of 40mg/d (p=0.001). Importantly, only in the 40mg/d treatment group the increase in FMD was significantly associated with baseline TC levels (r-0.57, p=0.004) and with creatinine clearance (r=0.61, p=0.002). Finally, only in the 40mg/d treatment group the association between creatinine clearance and FMD was significant even after adjustment for confounders such as TC, age, ejection fraction smoking habits, the presence of diabetes mellitus and hypertension [b=0.09, 95% CI (0.02-0.16), p=0.01].
Conclusions: In ischemic HF subjects both high and low dose atorvastatin treatment can improve inflammatory status and endothelial function. Importantly, the greatest improvement in endothelial function is observed in patients receiving high dose atorvastatin treatment with elevated baseline TC levels and preserved renal function.

P6325 | BEDSIDE
Prolonged heat stress as a factor of endothelial damage

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Objective: To study the effect of prolonged heat stress on endothelial function in healthy volunteers in the model experiment.
Materials and methods: Six healthy men (34,3±9,6) were isolated in a sealed housing unit for 30 days. Microclimate in the unit was maintained with day temperature in the range +30+38℃ (33,9±2,3) at a relative humidity of 30-50% (38,3±6,9) and a night temperature in the range +26+31℃ (28,1±1,5) at a relative humidity of 50-75% (68,5±7,1) that had simulated heat wave in July-August 2010 in Moscow. The study was performed in the skin microcirculation of the upper limbs by laser Doppler flowmetry (LDF) and capillaroscopy (CS) in the morning and evening every other day. Ultrasound echocardiography (echocardiography), finger photoplethysmography (PPG) and blood sampling for endothelial apoptosis CD31+CD41- microparticles was performed on the 10th, 20th and 30th experiment day.
Results: We observed marked intensification of skin blood flow which manifested in increase of capillary blood flow velocity more 3500 μm/sec and in widening of pericapillary zone, despite the pronounced shunting blood arteriolo-venular anastomoses. These changes had been found from the first day of the experiment, according to the LDF and the CS. On the 10th day of the experiment echocardiography revealed an increase in the left atrium group average from 55 to 69 ml (p<0.05), end diastolic volume of the left ventricle from 120 to 145 ml (p<0.05), stroke volume from 80 to 109 ml (p<0.05), the cardiac output from 5.2 to 6.2 l/min. The decrease of occlusion index to 50% was marked according to PPG. The results also show marked increase in the number of apoptotic endothelial microparticles CD31+ CD41- (up to 10,000 cells). All changes had been observed during the whole experiment.
Conclusion: The maintaining of the temperature homeostasis during prolonged heat stress is achieved through the increasing cardiac output with severe exacerbation of cutaneous blood flow. The prolonged hemodynamic microvascular overload during thermoregulation may be an independent damaging factor that contributes to the development of endothelial dysfunction.

P6326 | BEDSIDE
Markers of endothelial dysfunction in ocular Behcet's Disease

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Purpose: The etiology of Behcet's Disease (BD) is not clarified yet. Immunological and environmental factors, endothelial dysfunction (ED), and genetic susceptibility have been proposed. ED has been shown to be related with acute systemic inflammatory conditions and chronic systemic vasculitis. ED is also considered to play a pivotal role in the pathogenesis and propagation of vasculitis in BD. The aim of this study was to evaluate patients with BD for the presence of ED and inflammation by measuring asymmetric dimethyl arginine (ADMA), carotid intima media thickness (CIMT), epicardial fat thickness (EFT) and neutrophil-lymphocyte-ratio (NLR).
Methods: Thirty six ocular BD patients of which 17 had active ocular BD and 19 had inactive ocular BD, and 31 healthy control subjects similar with study group in terms of age, sex, body mass index and smoking status were recruited in this prospective, comparative study. All patients underwent transthoracic echocardiography and carotid Doppler ultrasound examination.
Results: The patients with BD were more likely to have higher white blood cell count, neutrophil counts, NLR, CIMT, EFT values and ADMA level. The other biochemical, hematological and echocardiographic parameters of the patients and healthy controls were comparable. The mean EFT value of the patients was significantly higher than the control group (5.0 0.8 vs. 4.0 0.4; p<0.001), and the NLR value of the patients was also significantly higher than the controls (3.6 1.7 vs. 2.6 1.2; p=0.007). Serum ADMA level was significantly higher in the patient group (3.2 0.5 vs. 2.0 0.8; p<0.001). CIMT was thicker in the patient group than that of healthy controls (0.52 0.09 vs. 0.42 0.03; p<0.001). The disease duration was positively correlated with the EFT and CIMT values (r: 0.406, p=0.014 and r: 0.477, p=0.003; respectively) in the patient group. We performed multivariate logistic regression analysis of ADMA level, NLR, CIMT and EFT values, which were found significant parameters in univariate analysis, and higher ADMA level (p=0.008) and CIMT values (p=0.025) were found to be associated with the presence of BD. The patients were categorized into two subgroups; active and inactive BD. In subgroup analysis; neutrophil count, NLR and ADMA level were significantly higher and the lymphocyte count was significantly lower in the active BD subgroup than inactive BD.
Conclusions: The present study highlights usefulness of serum ADMA level and noninvasive measurement of CIMT in evaluation of ED which is considered to play a pivotal role in the pathogenesis and propagation vasculitis in BD.

MISCELLANEOUS

P6328 | BEDSIDE
Constrictive pericarditis: a different perspective of the disease in cardiac magnetic resonance imaging era

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The aim of this study was to assess the progression of constrictive pericarditis (CP) based on the degree of pericardial inflammation as seen on Cardiac Magnetic Resonance (CMR) with Late Gadolinium Enhancement (LGE).
Between 2011-12, we identified 42 patients with echocardiographic & CMR evidence of CP who were treated with anti-inflammatory therapy. CMR LGE was graded qualitatively based on the intensity of LGE. We subdivided our patients based on their CMR LGE intensity as shown in Table 1. Clinical resolution was defined as improvement in NYHA class by 1.

Table 1

	None-Mild LGE (N=24)	Mod-Severe LGE (N=18)	P value
Age (mean±SD, years)	60±13	54±16	0.17
Male %	19 (79%)	15 (83%)	0.53
NYHA class median (10% to 90%)	3 (1–4)	2 (1–4)	0.007
Pedal edema	17 (71%)	5 (28%)	0.007
JVD	17 (71%)	6 (33%)	0.02
Etiology 0.48			
Idiopathic (n)	16	13	
Post pericardiotomy syndrome (n)	8	5	
Steroid n (%)	14 (58%)	15 (83%)	0.08
WSR (mean±SD, mm/hr)	16±21	34±35	0.057
US CRP (mean±SD, mg/L)	22.1±22.1	69±93	0.03

*Follow up echocardiogram was available for 21 & 15 patient in both groups respectively.

24 (57%) patients had None-Mild LGE (weak LGE) while 18 (43%) had Moderate-Severe LGE (Intense LGE). Patients with weak LGE tended to be worse clinically

on initial evaluation with a higher NYHA class, more pedal edema & JVD. Baseline inflammatory biomarkers tended to be higher in the intense LGE group. Clinical & echocardiographic resolution of CP after anti-inflammatory therapy was higher in the intense LGE group (83% vs 21%, P<0.001) at a mean follow up of 3.6±2 months. Pericardiectomy was done frequently in the weak LGE group (46% vs 17%, P=0.047). Multivariate analysis found intense LGE to be significantly associated with clinical/echocardiographic resolution of CP after adjusting for age (p=0.007)
Moderate to severe CMR LGE & high inflammatory markers are associated with milder clinical CP and responds to anti-inflammatory therapy.

P6329 | BEDSIDE
Association of aortic pulse wave velocity with NT-pro-BNP levels 12 months after acute STEMI

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Objectives: We have previously shown that aortic pulse wave velocity (PWV) is associated with biomarkers of myocardial wall stress measured 4 months after acute STEMI. We speculated that vascular-ventricular coupling might be responsible for these results. In the present study, we prospectively investigated the relationship of increased aortic stiffness with N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) levels 12 months after STEMI.
Materials and methods: 50 STEMI patients who were treated with primary coronary angioplasty underwent cardiovascular magnetic resonance (CMR) at baseline and at 12-month follow-up. Aortic PWV was determined by velocity-encoded, phase-contrast CMR. Blood samples were routinely drawn at baseline and follow-up to determine NT-proBNP levels. PWV and NT-pro-BNP levels were log-transformed for correlation analysis to achieve normal distribution.
Results: The mean age of the study population was 57±12 years and median baseline PWV was 7.0 m/s (IQR: 5.8 – 8.4). After 12 months mean infarct size was 11±6% of left ventricular mass and mean ejection fraction was 53±11%. The median NT-proBNP level after 12 months was 169 ng/L (IQR: 97 – 335). In univariate analysis NT-pro-BNP levels after 12 months correlated with PWV (r: 0.415, p=0.003), age (r: 0.427, p=0.002), end-systolic volume (r: 0.291, p=0.040) and infarct size (r: 0.460, p=0.001). After multivariate analysis PWV remained an independent predictor of NT-pro-BNP levels 12 months after STEMI (model: r: 0.742, p<0.001).
Conclusion: Aortic stiffness, as determined by PWV, is associated with NT-pro-BNP levels 12 months after reperfused STEMI. This association remains significant after correction for infarct size, age and end-systolic volume. Our data suggests a role for aortic stiffness in chronic left ventricular remodeling after STEMI.

P6330 | SPOTLIGHT
Deriving benefit from exercise-induced ischaemia in coronary artery disease patients? Investigation of warm-up angina with transmural perfusion gradients using high-resolution CMR perfusion

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Purpose: Warm-up angina describes a reduction in angina, ischaemia and arrhythmias on second exercise in patients with coronary artery disease, after "warming-up". The exact mechanism underlying this cardio-protection remains uncharacterised.
Cardiac magnetic resonance (CMR) compatible ergometers permit quantification of exercise-induced ischaemia, which is the most physiological method of inducing myocardial stress. Previous studies have demonstrated that transmural perfusion gradients (TPG) using high-resolution CMR allow discrimination between the subendocardium and subepicardium.
The purpose of this study was to test whether there is preferential redistribution of perfusion towards the vulnerable subendocardial layer on second exercise.
Methods: Coronary artery disease patients gave consent for supine cycle ergometry on the CMR scanner table (Lode, Netherlands), using a standardised incremental exercise protocol. High-resolution perfusion CMR was performed at each peak exercise stress on a 3T Philips Achieva® system using dual bolus 0.05 mmol/kg Gd-DTPA. 3 LV short-axis slices were acquired with saturation recovery gradient echo (repetition time/echo time 2.5ms/1.16ms, flip angle 15°, 2.4 x k-t SENSE acceleration, 11 interleaved training profiles, spatial resolution 1.2x1.2x10mm^3, 3 slices acquired at each RR interval, 120 dynamics). Rest perfusion was also performed.
Data were analysed with Philips EasyScil prototyping. Subendocardial and subepicardial borders were traced to obtain respective signal intensity (SI) curves. TPGs (mean gradient, threshold 5%) demonstrate the difference in contrast uptake between subendocardial and subepicardial layers over time. Data are presented as mean±SD.
Results: Ten patients (63.5±8 years) completed two consecutive periods of exercise (Ex1, Ex2), separated by a 20 min rest period. Time to angina increased on Ex2 (236 vs 173 seconds) despite similar myocardial oxygen consumption (rate pressure product Ex1 19,834 vs Ex2 20,288 mmHg/second). There was a significant increase in TPG between rest and Ex1 (10.74±4.7 vs 13.94±6.14, p=0.03), but no difference between rest and Ex2 (10.74±4.7 vs 11.71±6.51, p=0.38). In a subgroup of patients (n=7) there was a significant decrease in TPG from Ex1 to Ex2 (15.52±6.4 vs 13.2±6.23, p=0.04).
Conclusions: Transmural perfusion gradients during exercise-induced ischaemia can be quantified using high-resolution CMR. TPGs demonstrate the vulnerability of the subendocardial layer to ischaemia on exercise. Redistribution of perfusion on second exercise may account for cardioprotection seen in patients with warm-up angina.

P6331 | BEDSIDE
Reduced coronary flow reserve evaluated by phase contrast cine magnetic resonance imaging in patients with heart failure with preserved ejection fraction

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Background: Previous studies demonstrated that approximately 50% of patients with the clinical symptom of heart failure have preserved systolic left ventricular function, commonly recognized as a heart failure with preserved ejection fraction (HFpEF). As the precise mechanism underlying HFpEF is unclear, effective treatments have not been established in patients with HFpEF. Phase contrast (PC) cine magnetic resonance (MR) imaging allows for the assessment of coronary flow reserve (CFR) noninvasively. Although impairment of CFR is observed in various pathophysiologic conditions, CFR of HFpEF has not been fully investigated. The aim of this study was to assess the CFR in patients with HFpEF by using PC cine MR imaging.
Materials and methods: We studied 20 HFpEF patients (mean age: 75±6 years), 20 left ventricular hypertrophy (LVH) (mean age: 73±5 years) and 20 controls (mean age: 74±5 years). Coronary artery disease was not observed in all study subjects.
By using 1.5T MR scanner and 32 channel cardiac coils, cine MR images of left ventricle were acquired to assess the left ventricular (LV) systolic function. Breath-hold PC cine MR images of coronary sinus (CS) were obtained to assess the blood flow of CS both at rest and during adenosine triphosphate (ATP) infusion. CFR was calculated as CS blood flow during ATP infusion divided by CS blood flow at rest.
Results: LV ejection fraction was preserved in all subjects. (HFpEF: 60.4±8.7%, LVH: 60.3±9.0%, controls: 61.0±8.5%).
CFR was significantly reduced in patients with HFpEF compared with LVH patients (2.40±0.23 vs 2.58±0.15, p=0.006) and control subjects (2.40±0.23 vs 3.21±0.23, p<0.001). Significant negative correlation was observed between CFR by MRI and the ratio of early transmitral flow velocity to tissue Doppler early diastolic mitral annular velocity (E/e') by echocardiography (R=-0.52, p=0.044).
Conclusion: In patients HFpEF, CFR was significantly reduced in comparison to patients with LVH and controls. Decreased CFR was associated with the severity of diastolic dysfunction by echocardiography. The results in the current study indicated that the dysfunction of left ventricular microcirculation plays an important role for the pathophysiology in patients with HFpEF.

P6332 | BEDSIDE
Prognostic value of deformation analysis by speckle-tracking echocardiography and late gadolinium enhancement cardiac magnetic resonance in patients with acute myocardial infarction

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Aim: This study evaluated the prognostic value of 2-dimensional speckle-tracking echocardiography (STE) in patients with acute myocardial infarction (AMI) in comparison with late gadolinium enhancement cardiac magnetic resonance (LGE).
Background: Myocardial deformation analysis by STE has been shown to predict left ventricular (LV) functional recovery and remodeling after AMI.
Methods: A total of 96 patients (61±11 years) with first AMI (54 with ST-segment elevation myocardial infarction (STEMI) and 42 with Non-STEMI (NSTEMI)), all treated by primary percutaneous coronary intervention, were included. STE and LGE were performed within 48 hours after AMI. Peak global longitudinal strain was determined by STE and LGE was performed to define the amount of global myocardial scar. At 18 months follow-up the primary endpoint was assessed as a composite of all-cause mortality, revascularization, reinfarction and hospitalization for heart failure.
Results: During follow-up 24 patients reached the primary endpoint. In patients with STEMI, a peak global longitudinal strain <-17.2% had a sensitivity of 62.5% and a specificity of 76.1%, LGE had a sensitivity of 62.5% and a specificity of 73.9% considering a cut-off point of 8.5% to predict a primary event at 18 months follow-up. The accuracy to predict a primary endpoint was similar for STE compared with LGE (AUC=0.707 vs. 0.693, p=0.8913).

In patients with NSTEMI, a peak global longitudinal strain <-15.3% had a sensitivity of 87.5% and a specificity of 84.6%, LGE >13.6% had a sensitivity of 62.5% and a specificity of 88.5% to predict a primary endpoint at 18 months follow-up. The accuracy to predict a primary endpoint was also similar for STE compared with LGE (AUC=0.879 vs. 0.793, p=0.3021).
Conclusion: In patients with AMI, accuracy to predict a composite of all-cause mortality, revascularization, reinfarction and hospitalization for heart failure was comparable between STE and LGE.

P6333 | BENCH
Comparison of NOGA endocardial mapping with cardiac magnetic resonance imaging for determination of infarct size and infarct transmurality for intramyocardial injection therapy

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Introduction: Cardiac magnetic resonance imaging (cMRI) with late enhancement (LE) is the gold standard for the assessment of infarct size, infarct transmurality and left ventricular (LV) function. The NOGA® electromechanical mapping system is currently used for online evaluation of myocardial viability, segmental wall motion and for delineation of border zone of infarction for targeted catheter-based intramyocardial drug, gene and cell therapies.
Methods: Sixty domestic pigs underwent diagnostic NOGA endocardial mapping and cMRI with LE with a time difference between the two 3D images of 2±1 days 60 days after closed-chest reperfused myocardial infarction (MI). The infarct size was compared between the two images by LE of cMRI and delineating the infarct core of the unipolar voltage polar map. The sizes of transmural and non-transmural infarction were calculated from the cMRI transmurality and NOGA bipolar maps using a cut-off of signal intensity (SI) >75% and >25% (cMRI) and bipolar voltage values of <0.8 mV and <1.9 mV, respectively. Linear regressions analysis and Bland-Altman plots were used to discover correlations and systematic differences between the two images. Overlapping ratio of the transmural and combined transmural and non-transmural areas were calculated.
Results: Significant correlation between the 3D cMRI-LE and 2D NOGA unipolar voltage polar map-derived infarct size was found ($r=0.504$, $p=4.04\times10^{-5}$) with a mean difference of 2.82% of the LV surface. Significant association between the transmural and bipolar polar maps of cMRI and NOGA could be proven with an overlap ratio of 91.3% regarding transmural infarction ($r=0.727$, $p<10^{-5}$). The extent of the non-transmural infarction showed also strong correlation ($r=0.555$, $p=2.32\times10^{-5}$) between the two images. NOGA overestimated the transmural scar size with 6.81% of the LV surface, but slightly underestimated the size of non-transmural infarction (-3.04% of the LV).
Conclusions: Combining unipolar and bipolar voltage maps, NOGA endocardial mapping is useful to delineate the targeted zone of intramyocardial therapy and may predict accurately the size of transmural and non-transmural infarction, comparable to the gold-standard cMRI. This might be particularly useful in patients with contraindication for cMRI and designated for targeted intramyocardial regenerative therapy.

P6334 | BEDSIDE
Value of the diffusion-weighted magnetic resonance imaging and calculation of the apparent diffusion coefficient in differential diagnostics of the primary and secondary renoparenchymous hypertension

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Objectives: Recently, diffusion-weighted magnetic resonance imaging (DW-MRI) has emerged as a reliable method to differentiate between various functional renal abnormalities. There is a growing necessity to differentiate between primary and secondary causes of hypertension, especially in elderly patients who might have multiple co-morbidities. The purpose of our study was to assess the value of the DW-MRI and consecutive calculation of the apparent diffusion coefficient in differential diagnostics of the primary (essential) and secondary renoparenchymous hypertension caused by long-standing chronic glomerulonephritis.
Materials and methods: The study included 32 consecutive patients (17 women and 15 men) with hypertension. The patients were divided into 2 groups depending on the presence or absence of known chronic kidney disease, namely chronic glomerulonephritis, comparable by age, sex and level of the blood pressure. 1st group consisted of hypertensive patients with known chronic kidney disease; 2nd group – of hypertensive patients without any indications of kidney disease. 11 healthy volunteers entered the group of comparison. All patients underwent diffusion-weighted multi-section echo-planar MRI (b value=600 s/mm^2). In the axial ADC maps, rectangular regions of interest were placed in the cortex of each kidney. The ADCs of the kidneys were calculated. In addition, magnetic resonance angiographic technique (without the use of a contrast enhancement) was used to exclude the presence of renovascular hypertension (renal artery stenosis).
Results: There was a statistically significant difference between the ADC values of both kidneys in the 1st and 2nd group (2.65±0.21 vs 3.31±0.31; P<0.05), as well as between 1st group and the group of comparison (3.35±0.34; P<0.05) respectively. There was no statistically significant difference between the ADC values of both kidneys in the 2nd group and group of comparison (P>0.05).
Conclusion: Presence of secondary renoparenchymous cause of hypertension, namely chronic glomerulonephritis result in significant decrease of the ADC values calculated on DW-MRI in comparison with healthy volunteers as well as patients with primary or essential hypertension. DW-MRI and consecutive calculation of the apparent diffusion coefficient can be a valuable tool in differential diagnosis of primary essential and secondary renoparenchymous hypertension caused by long-standing glomerulonephritis as well as to determine the extent of target organ damage in patients with hypertension and underlying chronic kidney disease.

P6335 | BEDSIDE
Correlation between left ventricular diastolic pressures and E/E ratio-a simultaneous Doppler and catheterization study in 190 unselected patients: Are there gender differences?

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Purpose: Mitral E/E' ratio is recommended for detecting elevated left ventricular filling pressures. More recently, gender specific differences in E/E'ratios have been demonstrated. However, the influence of haemodynamic measurements is not clear. The aim of our prospective study was (1) to assess the usefulness of mitral E/E' ratio for predicting left ventricular filling pressures in an unselected group of patients undergoing cardiac catheterization and (2) to assess gender differences.
Methods: 203 unselected patients were chosen for simultaneous echocardiographic examination and cardiac catheterization. E/E' ratio was correlated with left ventricular enddiastolic pressures (LVEDP) pre and post laevocardiography. 190 patients had sufficient echogenicity to allow complete assessment of Doppler and tissue Doppler parameters.
Results: Overall, there was only a moderate significant correlation between E/E'ratio and LVEDP pre laevocardiography (R= 0.24). In patients with ejection fraction (EF) >50% there was no significant correlation. Female patients had higher baseline E/E' ratios than male patients. An E/E' ratio >15 for predicting an elevated LVEDP was only significant in male but not in female patients. Irrespective of gender, a stratification of E/E' ratio <8, 8-15 and >15 did not allow prediction of LVEDP.
Conclusions: In an unselected group of patients undergoing catheterization, E/E' ratio is only moderately correlated with LVEDP. There are significant gender differences and an E/E' ratio >15 predicted an elevated LVEDP only in male patients.

P6336 | BEDSIDE
Long-term prognostic impact of basal thinning of the interventricular septum in patients with cardiac sarcoidosis

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Purpose: Basal thinning of the interventricular septum (IVS) is one of the key findings for diagnosing cardiac sarcoidosis (CS). However, the long-term prognostic significance of the basal IVS thinning in CS remains unclear.
Methods: We examined 74 consecutive patients diagnosed as CS by clinical and/or pathological findings and clearly evaluated basal IVS by echocardiogram. We measured the thickness A which was 10 mm distant from the aortic annulus on the IVS and the thickness B which was the one-third point nearby the annulus, and calculated the ratio A/B. Patients were divided into two groups according to the presence or absence of basal IVS thinning, defined as thickness A ≤4 mm and/or ratio A/B ≤0.6, as previously reported.
Results: Basal IVS thinning was observed in 21 patients. Age, gender, LVEF, angiotensin converting enzyme, lysozyme activity and BNP levels, use of and dose of corticosteroid therapy were comparable between the two groups. During the follow-up (5.1±2.5 years), the presence of basal IVS thinning was associated with higher long-term adverse events including all-cause death, symptomatic arrhythmias, and heart failure admission (P=0.006, Fig. 1A). Multivariate analysis showed the presence of basal IVS thinning (HR 2.86, 95% CI 1.31–6.14) and use of corticosteroid therapy (HR 0.29, 95% CI 0.13–0.66) were independent determinants for long-term adverse events. Furthermore, patients with basal IVS thinning

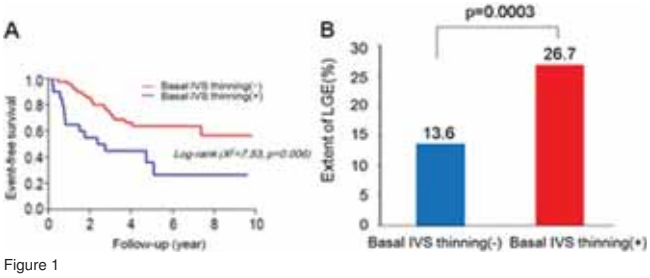

Figure 1

had larger extent of late gadolinium enhancement (LGE) than those without (27% vs 14%, P=0.0003, Fig. 1B).
Conclusions: Presence of basal IVS thinning was an independent determinant for poor long-term clinical outcomes with the larger extent of LGE, suggesting the basal IVS thinning could be a novel prognostic indicator in patients with CS.

P6337 | BENCH
Ultrasound diagnosis of pulmonary congestion in heart failure; simplified approach

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Pulmonary edema (PE), due to fluid retention and redistribution is the cardinal manifestations of heart failure (HF). The aim of this investigation was to study the effectiveness of simplified thoracic sonography in diagnosis of PE
Material and methods: 400 patients with II-IV NYHA functional class HF were evaluated (105 patients with diastolic and 295 with systolic HF). The control group consisted of 160 patients with different heart diseases (CHD, Hypertension, Aortic valve diseases), but without HF. Sonographic examination of a lung was done with 3,0-4,0 MgHz convex or sector probe, from 10 points on thoracic wall (cross points of midclavicular line with II, IV and V intercostal spaces and anterior axilar line with IV and V intercostal spaces), which corresponded to the projection of lower, middle and upper lobes of right lung and upper and lower lobes of left lung.
Results: During ultrasound examination 94.5% of patients with HF had "Comet tail phenomenon" (CTPh), which was registered only in 35,5% patients without HF ($p>0,001$). In DHF group CTPh was registered in 90,5% and in systolic HF group in 95,9% patients. In 91% of patients with HF CTPh was registered from 3 and more registration points. In control group CTPh was registered from more than 3 points only in 2 (1,3%) patients. The best results in diagnosis of DHF can be achieved if we take "3 and more registration points" as a reference point for diagnosis of pulmonary congestion (sensitivity - 0,911, specificity - 0,942, positive predictive value 0,975). The time of examination by simplified method for evaluation of CTPh and pleural space took 3-4 minutes.
Conclusion: In patients with HF during pulmonary ultrasound examination significantly often was registered CTPh. The count of registration points from the thoracic wall of CTPh 3 and $>$ is sensitive and specific sign of HF. The simplified thoracic ultrasound is highly effective in diagnosis of PE in patiets with HF

P6338 | BENCH
Tissue engineered pulmonary valved stent implantation in sheep: transthoracic echocardiographic evaluation (TTE)

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Purpose: Implanted tissue valves are prone to degeneration particularly in the adolescent. Tissue engineered valves in minimally invasively implanted stents may improve the durability. Thus implanted animals were followed up by transthoracic echocardiographic evaluation for up to six months.
Methods: Porcine pulmonary heart valves were decellularized, sutured into a cone shaped nitinol stent and seeded with autologous CD133+cells derived from the bone marrow of n=10 sheep (38.55±2.9 kg). The valved stents were implanted via transventricular approach in the beating heart. Transthoracic echocardiography was used for long term follow up of up to six months. Stent location, transvalvular gradients, valve morphology and function were assessed at different time points.
Results: Implantation was completed in eight of ten animals with orthotopic position achieved in 6 cases. Two animals were excluded due to ventricular fibrillation and stent dislocation during implantation. The echocardiographic examination in sheep was challenging due to the keel shaped thorax. Standard and non-standard views from both sides of the chest were necessary to obtain the desired parameters. During the observation period three animals had to be euthanized abortively due to stent migration. Average survival was 65±71 days. Two animals were followed up for 6 months.Thickening of the valve was observed in 2 of 5 animals. Valve insufficiency was not present shortly after implantation as confirmed by echocardiography and angiography. However increasing valve insufficiency was observed during the follow up of all (n=3) sheep $>$90 d. The mean pressure gradients increased during the follow up from 0.86±0.25 mmHg before implantation to 2.38±2.60 mmHg).
Conclusion: This study shows the feasibility of implanting a tissue engineered valved stent but identifies stent anchoring as a main challenge. The transvalvular gradients of the tissue engineered valves increased over time, but revealed no significant stenosis. Despite limitations in sheep TTE proved a valuable technique to determine stent position and valve function in this study.

P6339 | BEDSIDE
Impact of stress hyperglycemia on coronary microvascular function after acute myocardial infarction

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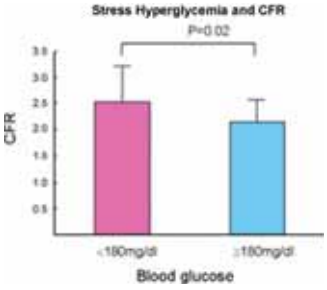
Background: Stress hyperglycemia (SH) is associated with adverse outcome and reduction in myocardial salvage after acute myocardial infarction (AMI). However, no relationship has been identified between admission blood glucose level and coronary flow reserve (CFR) as an index of microvascular function in patients with AMI.
Methods: This study assessed 73 consecutive patients with a first anterior AMI who underwent successful percutaneous coronary intervention within 24 h from onset of symptoms. Plasma blood glucose was measured on admission. SH was defined as blood glucose $\geq$10 mmol/L (180 mg/dl). We excluded the patients with a previous or current diagnosis of diabetes or an abnormal oral glucose tolerance test (OGTT, 75-g) 5 days after admission. CFR was calculated as the ratio of hyperemic, which was induced by intravenous adenosine administration, to baseline diastolic coronary flow velocity of the left anterior descending artery using transthoracic echocardiography 7 days after AMI.
Results: In 73 patients (mean age: 65 years, 48 males), 14 patients showed SH (218±48mg/dl). There was no significant difference in peak serum creatine phosphokinase between patients with (3012±2204IU/L) and without SH (2322±1837IU/L). Baseline diastolic coronary flow velocity in patients with SH (24±11cm/s) was higher than those without SH (19±6 cm/s, p=0.04), while there was no significant difference in hyperemic coronary flow velocity between the patients with (50±26 cm/s) and without SH (48±20 cm/s). Calculated CFR of the patients with stress hyperglycemia (2.0±0.4) was significantly lower than those without stress hyperglycemia (2.4±0.6, p=0.02).



Conclusions: Coronary microvascular function was severely impaired in patients with stress hyperglycemia after AMI.

MONITORING LEFT VENTRICULAR FUNCTION

P6341 | BEDSIDE
What does the mitral E/e' ratio represent in parameters of LV hemodynamics?

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Background: Conflicting evidence exists as to whether the mitral E/e' ratio can be a reliable predictor of the left ventricular end-diastolic pressure (LVEDP). Moreover, recently some study reported that the mitral E/e' ratio was better correlated with the pre-a diastolic pressure (LVDP) than LV end-diastolic pressure (LVEDP) in patients without heart failure (HF). Therefore, this study was aimed to investigate whether the value of the mitral E/e' ratio is a reliable predicator for the LVEDP estimation.
Methods: This study was composed of 218 patients who underwent left heart catheterization and Echo-Doppler exam at the same day. The pre-a LVDP was measured at the onset of the a-wave and the LVEDP at the nadir of "a"-wave before the rapid onset of isovolumetric LV pressure by automatically mechanic measurement. A pre-a LVDP $\leq$10 mmHg and a LVEDP $\leq$15 mmHg were considered normal. LV systolic dysfunction was defined as a $<$55% ejection fraction (EF).
Results: The E/A ratio were well correlated with the pre-a LVDP and the LVEDP. The septal E/e' ratio was better correlated with the LVEDP than with pre-a LVDP, irrespective of the LVEDP level or EF value. The septal E/e' ratio was significantly higher in decreased EF and in the dilated left ventricular (LV) geometry. No significant difference in mean LVEDP was found among the three groups with E/E' ratios of $<$8, 8-15, and $>$15. The sensitivity of septal E/E′ ratios $>$15 for predicting a $>$15 mmHg LVEDP were 42% and the specificity of was 71%. Also the septal E/E′ ratios $<$8 had sensitivity of 12% and specificity of 87% for predicting a $<$15 mmHg LVEDP.
Conclusion: Our study showed that the mitral E/e' ratio is better correlated with the LVEDP than with pre-a LVDP, irrespective of the presence of heart failure. However, as the mitral E/e' had low sensitivity and specificity for predicting increased LVEDP, the clinical value of mitral E/e' ratio is limited as a predictor of LVEDP.

P6342 | BENCH

Recovery of left ventricular systolic function after acute myocardial infarction: a comparative study between emergency percutaneous coronary intervention and fibrinolytic therapy

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Background: Myocardial injury after AMI is known to be a regional and heterogeneous process, so regional functional evaluation has been shown to provide additional important diagnostic and prognostic information to global function assessment.
Objectives: Quantitative assessment of the recovery of the regional and global left ventricular systolic function after reperfusion in acute myocardial infarction.
Methods: The study included 60 patients with first time acute myocardial infarction, thirty were treated with fibrinolytic therapy and 30 treated with emergency PCI. Evaluation was performed at 1 week and after 30 days by conventional echo (2D, MM, color and PW Doppler), by tissue Doppler image (mitral annular systolic velocity, Sa) and 2D strain (Global longitudinal peak systolic strain, GLPSS Results. 47% of the study populations were considered as having a significant recovery in systolic function by one month (60% of invasive subgroup, and 40% of those who had fibrinolysis). Conventional echo parameters showed insignificant difference neither from 1 week to 1month, nor between the two subgroups. There was significant improvement in Sa from 5cm/sec ±4 at 1 week to 7 cm/sec ±3 at one month, and was higher in invasive subgroup compared to pharmacological subgroup (8 cm/sec ±2 versus 5 cm/sec ±2, p=0.02).GLPSS showed significant improvement from -13.5% ±7at one week to -15% ±8 at one month. GLPSS was better in invasive group than in pharmacological one at baseline (-15.2%±5 versus -11.9%±4, p=0.04). At one month, GLPSS improved to -12%±4%, -16%±3 in the pharmacological and invasive subgroups respectively (p 0.04).
Conclusion: GLPSS and TDI parameters detected the recovery of LV systolic function after AMI.

P6343 | BEDSIDE

Estimation of the global peak left atrial longitudinal strain and peak left atrial longitudinal strain rate in patients with recurrent atrial fibrillation

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Purpose: To compare indices of the global peak left atrial longitudinal strain (globPALS) and peak left atrial longitudinal strain rate (PALSR) in chronic heart disease (CHD) patients with paroxysmal and persistent atrial fibrillation (AF).
Materials and methods: A total of 48 patients with the history of myocardial infarction (MI) (mean age 65±6 years, ejection fraction (EF) 58±8%) were divided into 2 groups: paroxysmal (n=22) and persistent (n=26) AF. Apical four- and two-chamber views images of 6 myocardial segments in the filling phase were obtained to assess globPALS; LA volume index (LAVI) was also calculated by biplane method. All measurements were performed in the sinus rhythm period.
Results: In the group of patients with paroxysmal AF globPALS was significantly higher as compared to patients with persistent AF (18,0±0,9 vs 15,2±2,3%, $p<0.005$). Patients with paroxysmal AF had higher PALSR than patients with persistent AF (2,06±0,14 vs 1,85±0,09 c 1 ($p<0.01$)), and lower LAVI (32±4 vs 48±11 ml/m ^{2} (p=0.001)). Also there was a significant inverse correlation between globPALS, PALSR and LVMM (r= -0.49 ($p<0.001$) and r= -0.42 ($p<0.007$), respectively), as well as between globPALS, PALSR and LAVI (r= -0.79 ($p<0.002$) and r= -0.84 ($p<0.003$), respectively).
Conclusions: Patients with persistent AF have a more significant increase in LP index, reduced both global peak left atrial longitudinal strain and peak left atrial longitudinal strain rate than patients with paroxysmal AF.

P6344 | BEDSIDE

Systolic and diastolic function by tissue Doppler imaging predicts adverse outcome in patients with atrial fibrillation

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Purpose: This study evaluates the prognostic value of TDI in patients with atrial fibrillation.
Methods: Echocardiograms from 313 patients with AF during examination were analyzed offline. The combined end-point was all-cause mortality, acute myocardial infarction, heart failure or stroke. Longitudinal systolic velocity (s') and early diastolic velocity (e') were measured by color TDI in six mitral annular sites and averaged to provide a global measurement of systolic and diastolic function. During a median follow-up of 898 days, 117 patients (37,4%) reached the combined end-point.
Results: TDI was significantly associated with the combined end-point, and the risk of reaching the combined end-point increased significantly with a decrease in s' and e' (Table 1). Even after adjustment for various risk factors and conventional echocardiographic parameters (LVEF and E/e'), the global TDI parameters remained independent predictors (Table 1). In contrast, LVEF and E/e' were not independent predictors of the combined endpoint in these models.

Table 1. Unadjusted and adjusted Cox proportional hazards regression models

Endpoint (64 events)	Hazard Ratio (95% CI)	P-value
Unadjusted model:		
s' per 1 cm/s decrease	1.34 (1.17–1.54)	<0.001
e' per 1 cm/s decrease	1.23 (1.13–1.34)	<0.001
E/e'	1.06 (1.03–1.09)	<0.001
Multivariable model adjusted for age, gender, heart rate, aortic stenosis, DM, LVEF and E/e':		
s' per 1 cm/s decrease	1.25 (1.02–1.25)	0.029
e' per 1 cm/s decrease	1.17 (1.03–1.33)	0.014

s': global peak systolic longitudinal mitral annular velocity determined by color tissue Doppler imaging; e': global peak early diastolic longitudinal mitral annular velocity determined by color tissue Doppler imaging; DM: diabetes mellitus; LVEF: left ventricular ejection fraction; E/E': transmitral to mitral anular early diastolic velocity ratio.

Conclusion: Both systolic and diastolic performance, as assessed by TDI, are strong predictors of an adverse outcome in patients with atrial fibrillation and are superior to conventional echocardiographic measurements of both systolic and diastolic function, that is, LVEF and E/e'.

P6345 | BEDSIDE

Clinical significance of simultaneous assessment of brachial intima-media thickness and flow-mediated dilation in patients with type 2 diabetes mellitus

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Purpose: Recently, measurement of flow-mediated vasodilation (FMD) has been widely used as a method for assessing vascular endothelial function. When measuring FMD in the brachial artery, intima-media thickness (IMT) can be assessed concomitantly in the same brachial artery using automatically vessel wall tracking system. Although the carotid IMT is reported to be associated with cardiovascular risk factors, there is limited data regarding brachial IMT. We, therefore, investigated clinical significance of brachial IMT combined with FMD in patients with type 2 diabetes mellitus (T2DM).
Methods: 159 patients withT2DM and 20 healthy subjects underwent FMD by ultrasound using 10-MHz linear array transducer. Brachial IMT was automatically measured on A-mode images of the far wall of the same right brachial artery. Serum markers including HbA1c, lipid profile, oxidative LDL, Lp(a), hsCRP, plasminogen activator inhibitor-1, and cystatin C were also measured. Left ventricular structure (left ventricular mass index [LVMI], left atrial volume index [LAVI]) and function (Early diastolic annular velocity [e']) were assessed using echocardiography.
Result: The measurement of brachial IMT was feasible in all subjects. The intra- and inter-observer correlation coefficients were considerable high (>0.9). Brachial IMT in patients with T2DM was significantly larger than that in the control group (0.35±0.02mm vs. 0.25±0.01mm, $p<0.01$). FMD in patients with T2DM was significantly lower than that in the control group (5.0±0.12% vs. 11.0±0.44%, $p<0.01$). In patients with T2DM, brachial IMT was significantly correlated with age (r=0.32, $p<0.01$), cystatin C (r=0.22, $p<0.01$), e' (r=0.22, $p<0.01$), and FMD (r=-0.29, $p<0.01$). There was a significant positive relationship between FMD was significantly correlated with age (r=0.62; $p<0.01$), cystatin C (r=0.16, p=0.04), e' (r=0.22, $p<0.01$), LDL-cholesterol (r=0.16, p=0.04), and HbA1 (r=0.22, $p<0.01$). However, there were no significant correlations of brachial IMT and FMD with HDL-C, oxidative LDL, Lp(a), hsCRP, plasminogen activator inhibitor-1, LVMI and LAVI.
Finally, patients were classified according to the median value of brachial IMT and FMD. There was no significant association of hsCRP with IMT and FMD, while patients with larger IMT and lower FMD showed the highest hsCRP levels compared to other groups (0.62±1.82mg/dl vs. 0.24±0.48mg/dl, p=0.04).
Conclusion: Brachial IMT is a marker of atherosclerosis and simultaneous measurement of brachial IMT and FMD could be informative for risk assessment of patients with T2DM.

P6346 | BENCH

Treatment with biological agents improves endothelial and coronary artery function in parallel with left ventricular deformation and twisting in patients with psoriasis

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The role of treatment with biological agents on vascular and LV function in psoriasis is unclear.
Methods: 101 patients (age: 50±12 yrs) with psoriasis (PS) (PASI disease activity score: 11.5±8) were randomized to receive an anti-TNF-a (n=32), an anti-IL12/23 regimen (n=31) or a combined cyclosporine and methotrexate (n=38). At baseline and after 4 months of treatment, we measured a) the carotid-femoral pulse wave velocity (Complior-PWVc) and augmentation index (AI) central systolic blood pressure (cSBP) and pulse wave velocity (PWVa) by Arteriograph; b) flow-mediated dilation of the brachial artery (FMD) and carotid intima-media thick-

ness (IMT); c) E'/A of mitral annular velocities, LV longitudinal (GLS, %), strain, twisting (Tw, deg), peak twisting (Tw, deg/sec) velocity, untwisting at mitral valve opening (unTw) and untwisting (unTw) velocity using speckle tracking echocardiography; d) coronary flow reserve (CFR). Forty normal subjects (N) served as controls.

Results: At baseline patients with psoriasis had higher PWVc, PWVa, AI, IMT, Tw,Tw velocity,unTw velocity and lower CFR, E'/A', GLS than normals (p0.05). risk factors age and sex were similar between the treatment groups. Four months post-treatment, patients treated with biological agents (n=63) had higher FMD (11±6 vs. 5±4), CFR (3.3±1.4 vs. 2.6±1), E'/A'(0.94±0.3 vs. 0.74±0.3) and reduced E/E' (8.3±3 vs. 9.4±3), Tw (15±6 vs. 17±9), Tw velocity (97±45 vs. 110±48), untwisting at mitral valve opening (8.3±3 vs. 9.4±3)and unTw velocity (100±44 vs. 120±60) (p 0.05 for all comparisons) showing values similar to those in controls (p=ns). No differences between anti-TNFa and anti-IL-12/23 were detected. Conversely, after treatment, patients on cyclosporine and methotrexate had no change in FMD (6.6±6 vs. 6.3±4), CFR (2.7±1.4 vs. 2.9±1), E'/A' (0.89±0.3 vs. 0.91±0.3) but an increase in AI (34±19 vs. 26±22), cSBP (135±22 vs. 128±15), Tw (15±5 vs. 13±6) and unTw velocity (110±59 vs. 98±55) (p 0.05 for all comparisons). PASI was similarly improved in all treatment arms

Conclusion: Treatment with biological agents improves endothelial and coronary microcirculatory function leading to improved LV myocardial deformation and twisting.

P6347 | BEDSIDE
Intra myocardiac adiposity is associated with left ventricular diastolic dysfunction without history of coroanry artery disease

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Background: Ectopic fat appositions such as visceral adipose tissue and epicardial adipose tissue are shown to be associated with left ventricular diastolic dysfunction (LVDD). In this study we evaluated the association between intra left ventricular myocardial fat (ILVMF) and LVDD in patients without history of coronary artery disease (CAD).

Methods: We retrospectively evaluated 1214 consecutive patients >20 years with coronary computed tomography (CT). Patients with LV ejection fraction <50%, severe valvular disease and history of CAD were excluded. Finally a total of 988 (age 64±13 years; 57% male) were included in the analysis. ILVMF was evaluated on unenhanced CT.

Results: Of 988 patients, 42 (4.3%) had ILVMF. The patients with ILVMI were elder (p=0.03) and had more prevalence of dyslipidemia (<0.01), diabetes mellitus (p=0.01), metabolic syndrome (p=0.03), higher triglyceride (p<0.01), and great use of statin (p<0.01) than patients without ILVMF. In echocardiographic parameters, e' as left ventricular diastolic parameter was significantly lower in patients with ILVMF than in patients without ILVMF (5.5±1.9 VS. 6.3±2.3, p=0.02), but no significant difference was found in LV mass index, LAVI. Multivariate logistic analysis revealed that ILVMF was independently associated with e' (table).

Multivariate logistic analysis

Variables	Univariate		Multivariate	
	odds ratio (95% CI)	p	odds ratio (95% CI)	p
e'	0.82 (0.69–0.96)	0.02	0.83 (0.70–0.99)	0.04
Age >65 y.o	1.42 (0.75–2.70)	0.28		
Gender	0.75 (0.40–1.39)	0.35		
Hypertension	1.72 (0.85–3.45)	0.13		
Dyslipidemia	2.54 (1.31–4.95)	<0.01	2.20 (1.12–4.32)	0.02
Diabetes mellitus	2.20 (1.18–4.09)	0.01	1.70 (0.90–3.21)	0.10
Visceral adipose tissue (/cm^2)	1.01 (1.00–1.01)	0.04	1.31 (0.70–2.46)	0.40

After adjustment for dyslipidemia, diabetes mellitus and visceral adipose tissue area, e' was significantly associated with existence of intra left ventricular myocardiac fat.

Conclusion: ILVMF was associated with LVDD in without history of CAD, suggesting that evaluation of ILVMF may be involved in a pathogenesis of heart failure with preserved ejection fraction.

P6348 | BEDSIDE
The missing links in missed transmissions of remotely monitored cardiovascular devices

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Introduction: Remote monitoring (RM) has become the standard of care for cardiovascular implantable electronic devices (CIED) follow up, promising time and cost saving while enabling timely decisions. However, troubleshooting missed transmissions consumes considerable resources. We prospectively assessed incidence and sources of failed remote evaluations.

Methods: Consecutive unique patients scheduled for remote follow up in the Cleveland Clinic Device Clinic were assessed on 12 randomly chosen weekdays over a 4 week period.

Results: 461 patients [307 implantable cardioverter defibrillator (ICD), 107 pacemakers (PM), 47 implantable loop recorders (ILR)] were evaluated. 193/461 (41.8%) failed remote follow-up on the appointed day. Of these, 109/193 (56.5%) followed with a delayed transmission (median 9 days) post-appointment; while 54/193 (27.9%) followed with an in-person visit (median 70 days). 28 patients (14.5%) did not follow-up at all over 18 months of follow-up. Scheduling errors accounted for 2/193 (1%) failures.

Failure of transmission was least likely on Mondays (36 out of 101 transmissions; 36.4%) compared to other weekdays. Likelihood of failure was similar in males 122/298 (40.9%) versus females 71/163 (43.5%) p=0.58; but varied between ILRs (29/47; 61.7%), pacemakers (54/107; 50.4%) and ICDs (110/307; 35.8%) p=0.0004, and was higher with inductive platforms [108/212; 50.9%] than wireless platforms [85/249; 34.1%] p=0.003.

There was no significant difference in missing RM between primary prevention versus secondary prevention ICDs [secondary prevention: 40/112 (35.7%); primary prevention: 70/195 (35.8%)], p=0.9743.

Trend of missed transmissions in CIEDs

	Implantable cardioverter defibrillator (n=307)	Pacemaker (n=107)	Implantable loop recorder (n=47)
Number who transmitted as per schedule	197	53	18
Number who failed scheduled transmission	110 (35.8%)	54 (50.4%)	29 (61.7%)

The table exhibits that ILRs were the worst in compliance, while ICDs were the best.

Conclusions: Even in centers practicing remote management as standard of care and maintaining excellent scheduling practice, failed scheduled evaluations occur frequently. Causes were technology related (wireless superior), device related (ILRs worst, ICDs best) and patient related. Attention to these factors may facilitate compliance with transmission, efficient workflow & timely resolution of actionable data.

P6349 | BEDSIDE
When a suboptimal biventricular pacing episode is too long?

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Aim: To assess the value of day by day remote monitoring in identifying prognostically critical burden of low biventricular pacing (CRT%).

Methods: Prospective, single-center registry encompassed 305 consecutive heart failure (HF) patients who were implanted with cardiac resynchronization (CRT-D) devices and subsequently monitored on a daily basis via remote monitoring for the median follow-up (FU) of 30.5 months. Low CRT pacing was defined as ≤95% CRT% within 24h. Patients have been stratified to 4 groups, according to quartile of cumulative time spent in low CRT%: quartile 1 (0 to 7 days), 2 (8 to 17 days), 3 (18 to 64 days) and quartile 4 (≥65 days).

Results: Long-term mortality and mean CRT% for the whole study population was 13.1% and 95.22% respectively. During the FU 63.2% of patients had at least one episode of low CRT pacing. None of the patients died, if the cumulative duration of low CRT% was within the range of 0-7 days (quartile 1). However, mortality rates for higher quartiles of low CRT% were significantly higher: 17.3 vs 14.0 vs 28.6% (quartile 2-4 respectively, all P<0.05 vs quartile 1). The prolongation of low CRT period (quartile 3 and 4) did not further increase mortality (both p=NS versus quartile 2). Adjusting for baseline confoundings, the cumulative low CRT pacing burden, but not duration of the longest episode of low CRT% was the independent risk factor for death. One additional day of low CRT% increased the risk of future death by 0.3% [HR 1.003; 95% CI 1.0001-1.006; p<0.05].

Conclusion: Cumulative CRT pacing≤95%, but not the longest episode of low pacing is an independent risk factor for death in CRT recipients. The cumulative burden of low CRT% lasting more than 7 days increase long-term mortality. Remote monitoring is a unique tool to monitor and detect low CRT periods with one day delay and thus allows to take urgent measures to regain the optimal biventricular stimulation.

P6350 | BEDSIDE
The clinical impact of telemonitoring for chronic heart failure: the RENEWING HEALTH project

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Purpose: To compare the clinical impact of remote monitoring (RM) with usual care (UC) of patients with chronic heart failure (HF).

Methods: The European RENEWING HEALTH Project aims to evaluate the clinical, organisational and economic effectiveness of RM in patients with diabetes, chronic obstructive pulmonary disease, implantable devices and HF in 9 European Countries. The patients with HF were randomly assigned (2:1) to RM or UC in multi-centre trial in the Veneto Region (Italy) and Central Greece. Inclusion criteria were: age >65 years and hospital discharge after acute heart failure in the previous three months and ejection fraction (EF) <40% or >40% plus BNP >400

pg/ml (or plus NT-proBNP >1500 pg/ml) during hospitalization. The primary outcome was the combined end point of all-cause mortality and hospitalizations for heart failure during the 12 month follow-up. Considering a 0.80 statistical power to demonstrate a 38% reduction of the primary end-point in RM group the sample size was 284 patients for the RM group and 142 for the UC group. The RM group was equipped to monitor blood pressure, heart rate, 1-lead ECG, pulse oxymetry and weight with triggers set according to individuals' personalised plan. Veneto sites have completed the predefined 9-months follow-up and we present these results.

Results: 188 (RM) and 97 (UC) patients were enrolled in Veneto. Baseline characteristics were similar in RM and UC group, except for some comorbidities, more frequent in the RM group: cerebrovascular disease in 18,6% vs 8,9% (p=0,04), diabetes in 38,8% vs 28,8% (p=0,04); atrial fibrillation was more frequent in UC group, 48% vs 43% (p=0,04). In both groups median age was 80 y, male gender was >60%, ischemic heart disease was the most frequent cardiac disease, more than 70% were enrolled because of elevated proBNP or BNP and other because of reduced EF, >93% were on diuretics, 70% on ACE-I or ARB, >65% on betablockers, >50% on aldosterone antagonists, 26% on digitalis, 48% on antiplatelets and 55% on anticoagulants. At the 9-month follow up the primary end-point was reached in 34,8% and 48,4% (p=0,04) of patients in RM and UC groups, respectively.

Conclusion: Although the results are preliminary, we have observed a significant reduction in combined end-point of all cause death and hospitalizations at 9 months in patients with HF randomized to telemonitoring service when compared to usual care. More data will be available in the next months when the clinical trial and the analysis will be completed.

MISCELLANEOUS – SPECT

P6352 | SPOTLIGHT
Increased rate of very low isotope-dose stress-only myocardial perfusion SPECT using CZT technology and quantitative analysis

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Purpose: To evaluate the feasibility and rate of very low isotope-dose (≤2mSv) stress-only (SO) myocardial perfusion SPECT (MPS) using CZT technology and quantitative analysis (QA) compared to conventional MPS.

Methods: We identified 4852 patients (2392 males, 49.3%) without CAD history, who underwent stress first Tc-99m sestamibi MPS between Feb 24 and Dec 25 2013. Acquisition was performed using a fast CZT camera (3255 patients 67.1%) and a conventional camera (1597 patients). Stress acquisition time of CZT and conventional was 5-7 and 16-20 minutes, respectively. CZT Tc-99m doses ranged 5-10 mCi stress/ 15-25 rest weight adjusted. Conventional doses were 10-13 stress/25-34 rest. QA (QPS, CSMC) utilized custom normal limits for the CZT and commercial for conventional camera. Total perfusion deficit (TPD) was derived. SO was based on visual analysis and QA.

Results: Stress dose of CZT MPS was 5-7 mCi (≤2 mSv) in 2757/3255 patients (84.7%) and ≤10 mCi (≤3 mSv) in 99.9%. Stress dose in the conventional MPS was 9-13 (3-4 mSv) in 1597 patients (100%). SO was more frequent among women than men, 1353/ 2460 (55%) vs. 691/ 2392 (28.9%), respectively, p<0.001. Among 2460 women, SO rates were higher in CZT vs. conventional MPS, 999/1699 (58.8%) vs. 354/761 (46.5%), respectively 0<0.001. Among 2392 men SO was more frequent in CZT compared to conventional, 499/1556 (32.1%) vs. 192/836 (22.9%), respectively p<0.001. Normal TPD (<5%) among women having SO was more frequent in the CZT compared to conventional MPS, 958/999 (95.9%) vs. 275/354 (77.6%), respectively p<0.001. Rate of TPD <5% among men performing SO was higher in CZT compared to conventional MPS, 479/499 (96%) vs. 165/192 (85.9%), respectively, p<0.001. Analysis by gender + BMI demonstrated higher rates of SO in the CZT vs. conventional in men and women with BMI≤30 or >30, with higher rates in women vs. men among BMI groups (Table).

Rates of stress-only by gender and BMI

	Men		Women	
	BMI ≤30	BMI >30	BMI ≤30	BMI >30
CZT	33.6% (425/1266)	25.5% (72/282)	62.7% (751/1198)	49.2% (241/490)
Conventional	25.6% (139/542)	18.5% (53/287)	53.8% (235/437)	36.1% (115/319)
p	0.01	0.043	0.01	<0.001

Conclusion: Very low-dose (≤2 mSv stress) CZT MPS provided higher rates of stress-only compared to conventional MPS in women and men across BMI groups, highly supported by normal quantitative analysis.

P6353 | BEDSIDE
The relationship between 99mTc-sestamibi washout and mitochondrial morphological changes in cardiomyopathy patients

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Background: Impaired myocardial retention of myocardial 99mTc-sestamibi (MIBI) scintigraphy reportedly reflects mitochondrial damage in various cardiac diseases. We investigated the relationship between the MIBI washout rate (WR) and mitochondrial morphological changes in comparison with the expression of messenger ribonucleic acid (mRNA) of mitochondrial electron transport-related enzymes in cardiomyopathy patients.

Methods: Forty cardiomyopathy patients, consisting of 20 hypertrophic cardiomyopathy (HCM) and 20 dilated cardiomyopathy (DCM) patients, were enrolled in this study. Resting myocardial MIBI scintigraphy was performed during overnight fast. Planar and single-photon emission computed tomography (SPECT) images were acquired. Quantitative MIBI WR was calculated on the early and delayed planar images. Biventricular cardiac catheter was conducted, and endomyocardial biopsy specimens were subsequently obtained for quantitative expression of mRNA using reverse transcription-polymerase chain reaction (RT-PCR) analysis and electron microscopic analyses.

Results: A significant reduction in the mRNA expression of mitochondrial electron transport-related enzymes [cytochrome c oxidase subunit 5B (COX5B), nicotinamide adenine dinucleotide dehydrogenase (ubiquinone) flavoprotein 3 (NDUFV3), α-ketoglutarate dehydrogenase (α-KGDH)] was found in both cardiomyopathy patients with an increased MIBI WR than in those without it. In electron microscopic analysis, a greater variation of mitochondrial size and more disorganized mitochondria were observed in HCM patients with an increased MIBI WR compared with those without it. Severely damaged mitochondria and glycogen deposition were more frequently observed in DCM patients with an increased MIBI WR than in those without it.

Conclusions: MIBI WR is associated with the severity of mitochondrial functional and morphological damage. Our results indicate that myocardial MIBI scintigraphy is a useful modality for assessing disease severity in cardiomyopathy patients.

P6354 | BEDSIDE
Diagnostic accuracy of the cadmium-zinc-telluride SPECT system using low-dose protocol with a short-scan time

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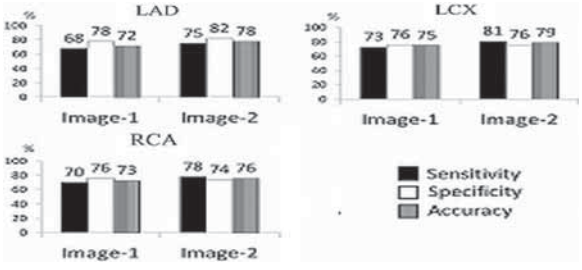
Background: Although low-dose stress myocardial perfusion imaging (MPI) using the cadmium-zinc-telluride (CZT) ultrafast camera system is reported to show adequate image quality, an optimal scan time has not been elucidated.

Methods: One hundred thirty patients underwent both low-dose stress/rest (185MBq/370MBq) 99mTc-tetrofosmin MPI using a Discovery NM 530c (46 patients with exercise stress, 84 with ATP stress) and coronary angiography (CAG) within 3 months. Image scan time was 10-min for stress and 6-min for at rest (Image-1). Subsequently, images were reconstructed to evaluate a shorter scan time (Image-2: 6-min for stress and 4-min for at rest), using a list mode on a Xeleris workstation. Sensitivity, specificity and accuracy of both Image-1 and Image-2 in detecting coronary artery disease (CAD) (>50% luminal narrowing) were analyzed on a per-vessel basis.

Results: CAG revealed significant CAD in 106 patients. Image-1 showed that respective sensitivity, specificity and accuracy were 68%, 78% and 72% for LAD stenosis, 73%, 76% and 75% for LCX stenosis, 70%, 76% and 73% for RCA stenosis, whereas Image-2 had higher sensitivity and accuracy without significant loss of specificity than Image-1 (respective sensitivity, specificity and accuracy were 75%, 82% and 78% for an LAD, 81%, 76% and 79% for an LCx, 78%, 74% and 76% for an RCA stenosis).



Conclusion: These results suggest that further reduction of either scan time or tracer dose may be possible for the CZT ultrafast camera system, even with the low dose protocol using 555 MBq of 99mTc-tetrofosmin.

P6355 | BEDSIDE

Real-time respiratory triggered SPECT myocardial perfusion imaging using CZT technology: impact of respiratory phase on CT attenuation correction

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Purpose: To assess the impact of the respiratory phase of real-time respiratory triggered SPECT acquisition on CT attenuation correction (CT-AC).
Methods: 40 patients underwent 1-day 99mTc-tetrofosmin pharmacological stress/rest myocardial perfusion SPECT imaging on a novel CZT gamma camera. SPECT was performed with free-breathing acquisition (unmatched) and with real-time respiratory triggering by intermittent acquisition confined to deep inspiration so as to match the respiratory phase of low-dose CT acquired for attenuation correction (phase-matched). Unmatched and phase-matched CT-AC SPECT were compared regarding visual diagnosis (scar and/or ischemia), segmental tracer uptake and image quality.
Results: Compared with unmatched CT-AC SPECT, applying CT-AC to respiratory phase-matched SPECT led to normalization (Fig. 1A) of presumed ischemia (Fig. 1B) in 3 patients and of scar in 1 patient. Thus, a change in diagnosis was observed in 4 patients (10%). Furthermore, phase-matched CT-AC SPECT showed a significant increase of relative segmental tracer uptake in inferobasal segments (mean difference ± SD: stress +3.2%±1.6 $p<0.05$; rest +3.6%±1.2 p=0.01) and significant reduction in apical and anteroseptal segments (ranging from -2.5%±1.0 to -4.4%±1.2, all $p<0.05$). Image quality scores improved significantly with phase-matched CT-AC-SPECT (mean difference ± SD: +0.5±0.7, p=0.001).

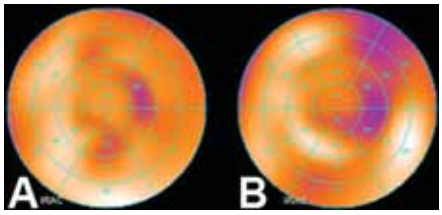

Figure 1

Conclusions: Compared to unmatched CT-AC SPECT, respiratory phase-matched CT-AC SPECT showed significant regional changes in tracer uptake, leading to a change in diagnosis in a significant amount of patients. Furthermore, image quality improved significantly, hinting at the potential of respiratory triggered myocardial perfusion SPECT in combination with phase-matched CT-AC.

P6356 | BEDSIDE

RETICARD SPECT sub-study: correlation between heart muscle perfusion and severity of hypertensive, diabetic or aterosclerotic retinopathy in patients with suspected stable coronary artery disease

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Purpose: The objective was to investigate whether microvascular disturbances of the retina in patients with suspected stable coronary artery disease, defined by retinal examination, can predict the existence of disturbances found on radio isotopic perfusion examinations of the heart muscle.
Methods: A total of 108 patients with suspected stable coronary artery disease were enrolled in the study. All patients underwent ophthalmologic examination and were classified in groups depending on their type and grade of retinopathy. After collecting general medical history and clinical data, 36 patients underwent heart muscle perfusion studies and then a coronary angiography, while 72 patients directly underwent a coronary angiography. Bruce protocol using a 12-lead electrocardiogram was performed. Single photon emission computed tomography (SPECT) was performed using a 48-hour protocol. At maximum stress, 99mTc-tetrofosmin was injected intravenously. After tracer injection, exercise was continued at the maximum workload for at least 1 min. Fixed and reversible perfusion defects were automatically quantified using the 20-segment model of the Quantitative Perfusion SPECT software. Each myocardial segment was visually scored using a 5-point scoring system: 0 normal, 1 mildly reduced, 2 moderately reduced, 3 severely reduced, and 4 absent. Total scores in 20 segments were calculated as the sum of stress, rest and difference scores. Attenuation correction was performed. Data End-diastolic volume, end-systolic volume and ejection fraction for stress and rest were computed with the Quantitative Gated SPECT software.
Results: In the group of patients with a high grade of hypertensive retinopathy, the impairment of the heart muscle perfusion at stress and rest was more frequent than in the group of patients with a low grade of hypertensive retinopathy (41.1% versus 32.4%, p=0.027). Similar data were observed in patients with atherosclerotic retinal microvascular disturbance (61.8% versus 0, p=0.001). Analysis of the heart muscle perfusion results showed a significant relationship with the severity of microvascular complications observed in eye fundus examinations.
Conclusions: Comprehensive ophthalmologic assessment of the progression of cardiovascular risk factors affecting the retina in patients with suspected coronary artery disease may be an indicator of heart muscle perfusion disturbance.

P6357 | BEDSIDE

Very low isotope-dose stress-first myocardial perfusion imaging using fast SPECT technology: correlation to invasive coronary angiography

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Purpose: To assess the diagnostic value of very low isotope-dose stress-first myocardial perfusion SPECT (MPS) in identifying significant coronary artery disease (CAD) using invasive coronary angiography (ICA) as gold standard.
Methods: We identified 118 consecutive patient (98 males, 83.1%) who underwent a very low isotope-dose stress-first Tc-99m sestamibi myocardial perfusion SPECT (MPS) using fast CZT technology, and were referred to invasive coronary angiography within 60 days following nuclear testing. Of these 87 (71 males, 81.6%) did not have history of myocardial infarction or coronary bypass surgery and were included in the final anlysis. Tc-99m doses ranged 5-10 mCi stress/ 15-25 rest, weight adjusted. Acquisition protocol consisted of stress supine, stress prone and rest supine 5-7, 3-4 and 2-3 minutes, respectively. Quantitative analysis (QPS, CSMC) of MPS utilized custom developed normal limits specific for the CZT camera. Summed stress score (SSS%) supine, SSS% prone, total perfusion deficit (TPD) supine, TPD prone and %ischemia (change from QPS) were autumatically derived. Significant coronary disease by ICA was defined as ≥70% stenosis.
Results: Stress dose of Tc-99m was ≤6 mCi (≤1.8 mSv) in 61 patients (74.4.%). Maximal stress dose was 10 mCi (3 mSv) injected to 5 patients with BMI 32-39. Significant coronary disease in ICA was found in 61/ 87 patients (70.1%). ROC analysis demonstrated area under the curve (AUC) higher than 0.8 for all quantitative parameters (Table). Prone variables SSS% prone and TPD stress prone yielded slightly larger AUC. A threshold for abnormality ≥4.5% yielded Sensitivity/ specificity for SSS% supine 75.4/73.1, TPD supine 75.4/ 69.2, change% 82/ 76.9, SSS% prone 78.9/ 78.3, and TPD prone 82.5/ 73.9.

Results of ROC analysis

	SSS% supine	TPD supine	Change	SSS% prone	TPD prone
Area	0.845	0.831	0.831	0.870	0.872
p	<0.001	<0.001	<0.001	<0.001	<0.001
95% CI	0.763–0.928	0.745–0.917	0.741–0.922	0.781–0.959	0.7850.959

Conclusion: Very low isotope-dose stress-first MPS using fast CZT technology provided high diagnostic value with reduced patient radiation exposure.

P6358 | BEDSIDE

Myocardial perfusion SPECT imaging versus invasive fractional flow reserve: a comparison between conventional SPECT and cadmium-zinc-telluride based SPECT

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Purpose: Recently introduced cardiac SPECT cameras with cadmium zinc telluride-based (CZT) detectors may provide superior image quality allowing faster acquisition with reduced radiation doses. Although concordance between SPECT and invasive fractional flow reserve (FFR) measurement has been studied, concordance of conventional and CZT-based SPECT with FFR has not been compared. Therefore, we prospectively assessed the level of agreement for conventional and CZT SPECT with FFR in patients with stable coronary artery disease.
Methods: Both invasive FFR and myocardial perfusion imaging using conventional and CZT SPECT were performed in 100 patients with stable angina and intermediate grade stenosis at invasive coronary angiography. A cut-off value of <0.75 was used to define abnormal FFR.
Results: Mean age was 64±11 years, 64% were male. Thirty-one percent had ischemia as demonstrated by SPECT, 20% had FFR <0.75. On a per-patient basis the concordance with FFR was 70% for conventional SPECT and 73% for CZT SPECT (p=0.627).
Conclusions: Only 20%-30% of patients with intermediate coronary stenoses have significant ischemia as assessed by SPECT or invasive FFR. The agreement between SPECT and FFR is modest and is similar for conventional and CZT SPECT. Further investigations are particularly necessary in patients with discrepant SPECT and FFR results, especially to determine whether these patients should undergo revascularisation.

P6359 | BEDSIDE
Progressive reduction in positive ischemic gated-SPECT studies in the last years

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Purpose: Different studies have shown a progressive reduction in the number of positive ischemic gated-SPECT studies. Our objective was to analyze the evolution of the gated-SPECT results performed in our Hospital.
Methods: During a period of 11 years, 10529 gated-SPET of myocardial perfusion were performed in our Nuclear Cardiology Unit. We evaluated the number of rest tests and stress-rest tests, and the presence of myocardial ischemia (differential stress score >2) in intervals of years according to the population age.
Results: There were 7.5% (n=785) of rest studies while 92.5% (n=9744) were stress-rest studies. Myocardial ischemia was detected in 17.6% (n=1712) of them. The table shows the studies performed in the different periods evaluated (*Lineal positive and significant relation, F: 145,183; p<0,001/**Lineal tendency, χ^2: 157.699; p<0,001/***Lineal tendency, χ^2: 84.828; p<0,001).

Studies performed

	Periods of years				
	<1997 n=1213	1997–2000 n=1990	2000–2003 n=2584	2003–2006 n=2350	2006–2008 n=2392
Age (years)*	60.7±11	63±11	63.8±12.2	64.5±11.6	65.6±13
Age > 70 years (%)*	283 (23.3)	590 (29,6)	902 (34.9)	876 (37.3)	1013 (42.3)
Rest studies (%)	81 (6.7)	238 (12)	215 (8.3)	116 (4.9)	135 (5.6)
Stress–rest (%)	1132 (93.3)	1752 (88)	2369 (91.7)	2.234 (95.1)	2.257 (94.4)
Presence of ischemia (%)**	228 (20.1)	426 (24.3)	429 (18.1)	350 (15.7)	279 (12.4)

Conclusions: The proportion of rest and stress-rest gated-SPECT studies along the last years did not change, while the number of studies with myocardial ischemia has been reduced significantly although the population age evaluated has increased.

P6360 | BEDSIDE
Myocardial perfusion imaging is low yield to assess for occult ischemia in patients with atrial fibrillation

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Purpose: The value of myocardial perfusion imaging (MPI) to evaluate for myocardial ischemia in patients with atrial fibrillation is uncertain. These patients often routinely undergo stress MPI. We hypothesize that MPI is low yield in this setting.
Methods: We identified 942 consecutive patients with atrial fibrillation who were referred for MPI for arrhythmia evaluation from October 2006 through June 2012. As outcomes, we assessed MPI results, revascularization within 6 months of MPI, and all cause mortality. MPI was considered abnormal if ejection fraction was less than 45% or if there were perfusion defects at rest or stress not attributed to artifact.
Results: Our patients were elderly (69.5±10.1 years), mostly male (63.1%), and some had known CAD (23.1%). 19.6% of MPI tests were abnormal, but only 4.3% demonstrated ischemia as defined by a summed difference score ≥4. Rates of obstructive CAD and revascularization were also low with only 7 patients receiving percutaneous coronary interventions (Fig. 1). Five of these patients had known CAD. After a follow-up of 2.9±1.7 years, there were 62 deaths (6.6%). Reversible perfusion defects did not predict mortality (univariable HR 0.49, 95% CI 0.12 to 1.32). Utilizing Cox proportional hazard modelling, only age (HR 1.05, 95% CI 1.02 to 1.08) and abnormal ejection fraction (HR 2.62, 95% CI 1.39 to 4.62) predicted mortality.

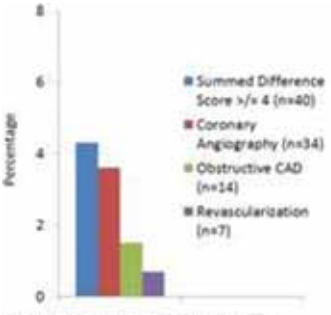

Figure 1. MPI, coronary angiography and revascularization results in patients with atrial fibrillation (n=942).

Conclusions: MPI offers low yield and failed to risk stratify these patients. MPI should thus be considered rarely appropriate as part of a routine evaluation in patients with atrial fibrillation. Testing should be reserved for patients with chest pain or other symptoms considered an ischemic equivalent.

P6361 | BENCH
Novel baseline correction method for quantitative analysis of myocardial perfusion from dce-cmr data using steady state T1 relaxation enhancement

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MR perfusion imaging enables quantitative estimation of myocardial blood flow (MBF). However the time interval between stress and rest imaging is insufficient for complete wash out of the first dose of contrast agent resulting in increase of the baseline signal intensity (SI) in the second data acquisition round and reducing quantification accuracy. Baseline correction usually is performed by using the pre contrast baseline SI level (MBFPC). Here we introduce a novel inter subject T1 baseline correction method.
Perfusion data were obtained from a hardware perfusion phantom with known perfusion values (1 and 2 mL/g/min). Images were acquired for different T1 baseline levels obtained by recirculating water and Gadolinium in the phantom after each of 4 consecutive injections. Images were acquired on a Philips Achieva 3T (TX) system. T1 mapping was performed using a MOLLI sequence. T1 weighted images are acquired before and after passage of the bolus of contrast to measure myocardial blood volume (MBV). MBF was estimated by Fermi deconvolution. A correction factor (CF) was calculated as CFi=MBV1st /MBV ith, i=2...4 and was used to correct MBF values (MBFCorr).
Figure 1 compares the MBFCorr with the MBFPC and the MBF before baseline correction. The MBFCorr values are in close agreement with the actual 1 and 2 mL/g/min perfusion rates (1.12±0.06 and 2.3±0.09 mL/g/min) compared with the non corrected MBF (1.5±0.4 and 2.8±0.3 mL/g/min) and MBFPC (0.8±0.07 and 2.3±0.3 mL/g/min). MBFCorr showed less variability (Coefficients of variation for 1 and 2 mL/g/min: MBFCorr 0.07 and 0.03; MBFPC 0.09 and 0.15; MBF 0.31 and 0.13).

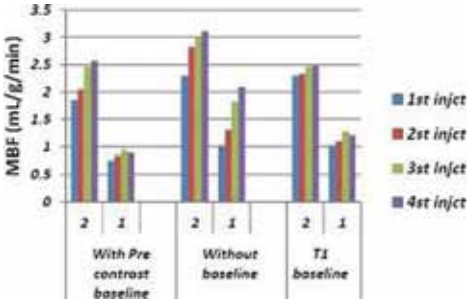

Figure 1

MBF estimates are strictly dependent on baseline SI values. T1 baseline correction allowed more precise perfusion estimation in comparison with pre contrast baseline correction.

MISCELLANEOUS – MIXED

P6363 | BENCH
Palpating the heart: in vivo cardiac time harmonic elastography under guidance of b-mode ultrasound with real time elastographic feedback

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Background: Cardiac MR elastography (cMRE) was recently shown sensitive to diastolic dysfunction. cMRE measures the periodic alteration of the myocardial shear modulus based on externally induced low-frequency acoustic vibrations produced by a loudspeaker. It was demonstrated that shear waves amplitudes are reduced in patients with pathologically increased myocardial stiffness (Fig. 1a). Purpose of this feasibility study is to adopt the principles of cMRE by fast and cost-efficient echocardiography.
Methods: Cardiac time-harmonic elastography (cTHE) was implemented into a commercial ultrasound B-mode scanner connected to a vibration bed designed to introduce 30-Hz continuous vibrations into the patient's chest (Fig. 1b). The alteration of shear wave amplitudes was displayed in real time after placement of the elastographic processing window of 1–2 cm width by B-mode guidance. In a group of 9 healthy volunteers, we focused on three different regions of the heart – the lateral wall of the left ventricle (LV), the right ventricle's wall (RV wall) and the blood pool of the right ventricle (RV lumen, Fig. 1c).

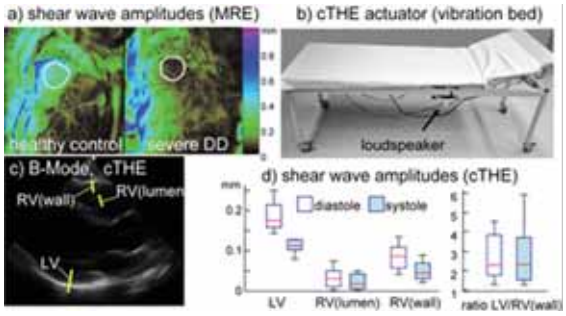

Figure 1

Results: Fig. 1d summarizes shear wave amplitudes in all three regions during diastole and systole. In agreement to cMRE, wave amplitudes are lower in systole than in diastole due to higher myocardial stiffness. Corresponding to cMRE, LV-shear wave amplitudes were normalized to RV amplitudes. The resulting ratios indicate low shear wave attenuation within LV correlated to asymptomatic myocardial mechanics and healthy elasticity relaxation.
Conclusion: We have demonstrated the feasibility of real time cTHE – a novel modality to palpate the heart by gentle shear vibrations applied in echocardiography. The measured wave amplitudes provide the reference values for diagnostic applications of cTHE.

P6364 | SPOTLIGHT
Diffusion-weighted magnetic resonance imaging in patients with arterial hypertension and known diabetic kidney disease: value of the apparent diffusion coefficient calculation

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Objectives: Unlike the majority of patients with uncomplicated hypertension in whom minimal renal damage develops in the absence of severe blood pressure elevations, patients with diabetic chronic kidney disease exhibit an increased vulnerability to even moderate blood pressure elevations. Recently, diffusion-weighted magnetic resonance imaging (DW-MRI) was used to differentiate various functional renal abnormalities. The reproducibility and feasibility of the DW-MRI of the kidneys in healthy volunteers and in patients with renal abnormalities has been reported. The purpose of our study was to assess the value of the diffusion magnetic resonance imaging of the kidneys and consecutive calculation of apparent diffusion coefficient in patients with arterial hypertension and known diabetic kidney disease.
Materials and methods: The study included 37 consecutive patients (19 men and 18 women) with hypertension. The patients were divided into 2 groups depending on the presence or absence of known diabetic kidney disease, comparable by age, sex and level of the blood pressure. 1st group consisted of hypertensive patients with known diabetic kidney disease; 2nd group – of hypertensive patients without known diabetes mellitus. 11 healthy volunteers entered the group of comparison. All patients underwent transverse diffusion-weighted multi-section echo-planar MRI (b value=600 s/mm^2). The ADCs of the kidneys were calculated.
Results: There was a statistically significant difference between the ADC values of both kidneys in the 1st and 2nd group (3.01±0.19 vs 3.29±0.24; $P<0.05$), as well as between 1st group and the group of comparison (3.37±0.38; $P<0.05$) respectively. There was no statistically significant difference between the ADC values of both kidneys in the 2nd group and group of comparison ($P>0.05$). In addition, the ADC values of patients with microalbuminuria did not differ from those of the other patients ($P>0.05$).
Conclusion: Target-organ damage caused by hypertension on the background of underlying diabetic chronic kidney disease significantly affect the ADC values calculated on diffusion-weighted magnetic resonance imaging in patients with known diabetic kidney disease. Despite the target-organ damage caused by hypertension, it did not affect the ADC values in patients without known diabetic kidney disease. Diffusion-weighted magnetic resonance imaging and consecutive calculation of the apparent diffusion coefficient can be a valuable tool to determine the extent of target organ damage in patients with hypertension and underlying diabetic chronic kidney disease.

P6365 | BEDSIDE
Quantified coronary frequency domain optical coherence tomography signal analysis for the evaluation of erythrocyte-rich thrombus: ex-vivo validation study

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Introduction: Frequency domain optical coherence tomography (FDOCT) can detect the coronary thrombus. Previous study has demonstrated that erythrocyte-rich thrombus contains more inflammatory cells and reflect high thrombus burden, leading to impaired myocardial reperfusion in myocardial infarction patients. The goal of this study is to investigate the utility of quantified FDOCT signal analysis in evaluating the erythrocyte-rich thrombus with ex-vivo materials.
Methods: We evaluated 54 specimens of coronary artery thrombus obtained by thrombectomy from 9 patients (myocardial infarction: 8, stent thrombosis: 1) who underwent primary percutaneous coronary intervention. The thrombi were immersed in saline immediately after the thrombectomy and FDOCT image acquisition was performed during automatic-pull back at 20 mm/s and 100 frames/s. Quantitative FDOCT analysis for all contiguous frames was performed by the dedicated automated software (OCT system software, Light Lab Inc.; figure). In each sample, signal intensity and normalized standard deviation of signal (NSD) were evaluated quantitatively for a frame showing the biggest thrombus area. All thrombi were stained with hematoxylin –eosin, and the cellular component of erythrocyte were analyzed using monoclonal antibodies against a protein specific to erythrocyte membranes (glycophorin-A) to enable automatic extraction of erythrocyte. Computer-assisted analysis was performed using dedicated software (WinROOF, Mitani Corp., Tokyo, Japan; figure) for color identification of the erythrocyte area.
Results: Erythrocyte-rich thrombus, defined as %erythrocyte area (erythrocyte area/total areaX100)≧33%, showed high NSD / mean signal intensityX100 (4.11±0.66 vs. 3.62±0.73, p=0.015). The optimal cut-off point of NSD/mean signal intensityX100 for prediction of erythrocyte-rich thrombus was 4.20 (sensitivity: 51.5%, specificity: 80.9%, area under the receiver operating characteristic curve: 0.67, respectively).
Conclusions: The present ex-vivo study showed the utility of quantified FDOCT signal analysis on the detection of erythrocyte-rich thrombus. Quantified FDOCT signal analysis may scrutinize the pathogenesis of acute coronary syndrome.

P6366 | SPOTLIGHT
Methods for image-based three-dimensional reconstruction of infarct-derived scars to locate conducting channels as radiofrequency ablation targets

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Purpose: Conducting channels (CCs) are responsible for the initiation and maintenance of infarcted-derived ventricular tachycardia (VT). It is necessary to accurately locate CCs to finish infarct-derived VT by radiofrequency ablation (RFA). It is not possible to detect CCs by evaluating only a few 2D DE-MRI (delay enhancement-MRI) slices. For detecting CCs it is necessary to build a 3D reconstruction of the anatomy of the left ventricle (LV) and of the infarct scar (core and border zone (BZ)) from a high-resolution DE-MRI stack. There is no consensus about which of the semi-automatic existing methods to delineate infarct scars from DE-MRI is more accurate or about the thresholds to apply for properly differentiating between core, BZ and healthy myocardium.
Methods: We have constructed a patient-specific 3D bi-ventricle model by manual delineation from a high-resolution DE-MRI stack including several 3D reconstructions of the ischemic region obtained from eight different semi-automatic algorithms.
Results: Figure 1 shows the 3D reconstructions of the scar obtained by different methods and different thresholds for the same method. The geometry and the volume of the scar depend strongly on the chosen method and thresholds.

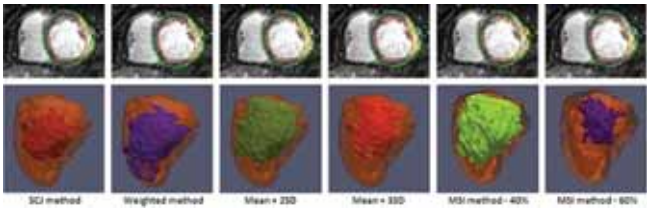

Figure 1. Different 3D reconstructions of infarct scar using some of the tested methods and thresholds. Top row shows the same short axis DE-MRI slice (mid-ventricular level) with manually drawn epicardial (green) and endocardial (red) contours and semi-automatic delineation of the ischemic zone (yellow). Bottom row shows the 3D bi-ventricle model (semi-transparant orange) including the 3D reconstruction of the scar from each method and threshold.

Conclusions: When different 3D reconstructions of the scar are compared by visual inspection, it is clear that the number, size and location of detected CCs are strongly method-dependent. We have visually compared the segmented geometries to electroanatomical voltage maps (EAMs) of endocardium and epicardium of the same patient, but it is difficult to drag consistent conclusions. It is necessary to carry out a larger study involving DE-MRI images from several patients and using a more objective methodology capable of comparing 3D segmented scar volumes to 2D high-density EAMs.

P6367 | BEDSIDE

The volume of left atrium measured by multi-detector computed tomography can predict of long term outcome in catheter ablation of atrial fibrillation

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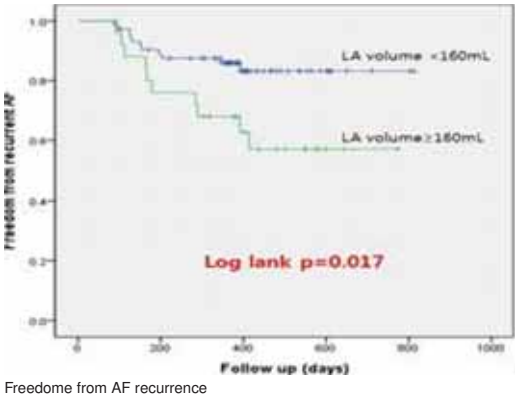
Background: This study aimed to identify the volume left atrium (LA) and left atrial appendage (LAA) calculated by multidetector computed tomography (MDCT) is related to the long term out come of radiofrequency catheter ablation (RFCA) for atrial fibrillation (AF).
Methods: We analyzed data from 99 consecutive patients who referred for RFCA due to drug-refractory symptomatic AF (age 56±10 years; 74% men; 64% paroxysmal AF). Prior to the procedure, all patients underwent ECG-gated 128 channels MDCT scan for assessment for PV anatomy, LA and LAA volume estimation, and electro-anatomical mapping intergration.
Results: The volume of LA and LAA calculated by CT was 142.6±32.2 mL and 14.7±6.0 mL, respectively. LA volume was smaller in paroxysmal AF (PAF) than persistent AF (PeAF) (133.9±29.3 mL vs. 158.0±31.4 mL, p<0.0001) but LAA volume was not significantly different between PAF and PeAF (13.9±5.0 mL vs. 16.3±7.3 mL, p=0.09). Patients were classified into 2 groups by the LA volume of 160mL; group 1 (LA volume <160mL,n=73) and group 2 (LA volume ≥160mL, n=26). After a mean follow up 12.6±5.3 months, 78.8% of the patients maintained sinus rhythm after the index ablation. AF free survival was significantly greater in group 1 than group 2 (84.9% vs. 61.5% p=0.017). No relationship was found between LAA volume and the outcome of RFCA. Multivariate analysis showed that the LA volume >160mL was an independent predictor of arrhythmia-free after ablation (Hazard ration 2.55, 95% confidential interval 1.02-6.35, p=0.045)



Freedome from AF recurrence

Conclusion: Higher LA volume is independent risk factor for AF recurrence after RFCA but not LAA volume. The LA volume quickly assessed by MDCT could be a good predictor of long term recurrence after AF ablation.

P6368 | BEDSIDE

The economic results of the CAPP study

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Purpose: To determine the most cost-effective diagnostic pathway for stable chest pain patients between cardiac computerised tomography (CT) and exercise stress electrocardiography testing (EST).
Method: A UK prospective randomised controlled trial of 500 troponin negative, stable chest pain patients without known coronary artery disease. Patient healthcare resource use (GP & nurse visits, emergency department (ED) visits, hospital investigations, hospital admissions and outpatient visits) was collected over the 12 month study period and total costs calculated per patient. Patient health related quality of life was measured using the EQ-5D administered at baseline, 3, 6 & 12 months and converted to utility scores for the calculation of Quality Adjusted Life Years (QALYs).
Results: 12 patients withdrew, resulting in 245 in the EST cohort and 243 in the CT cohort, with no significant difference in baseline demographics. There were increased revascularisation in the CT arm, but increased ED attendances with more associated admissions in the EST. Mean (95% CI) total costs for the CT and EST groups were £2034.80 (1591.81 to 2477.80) and £2031.60 (£1522.21 to 2540.99) respectively. The small difference in total mean costs was not statistically significant (p=0.992). Mean (95% CI) QALYs for CT and EST were 0.81 (0.78 to 0.84) and 0.79 (0.76 to 0.83) respectively. The small difference in QALYs of 0.02 (bootstrapped 95% CI -0.02 to 0.06) was not statistically significant (p=0.443). A complete case analysis using linear regression to adjust costs and QALYs for age, sex, type of pain (non anginal/typical/atypical) and baseline health related quality of life (baseline EQ-5D utility score) was then performed. A mean total cost difference of -£50.41 (bootstrapped 95% CI -664.14 to 563.31) was observed indicating a small cost saving. The mean QALY difference remained 0.02, with neither statistically significant (p=0.872 and p=0.988 respectively). Multiple imputation was used to impute values for the unobserved total cost and QALY data and costs and QALYs were again adjusted for age, sex, type of pain (non anginal/typical/atypical) and baseline EQ-5D utility score using linear regression. This showed a mean total cost difference of -£65.35 and a mean QALY difference of 0.01 which were not statistically significant. A cost effectiveness acceptability curve indicated that at a willingness to pay threshold of £20,000/QALY, cardiac CT had an 80% probability of being more cost-effective than EST.
Conclusions: The use of cardiac CT was more cost effective than EST, with associated clinical benefit.

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Lateral myocardial infarction generates prominent R wave in V1

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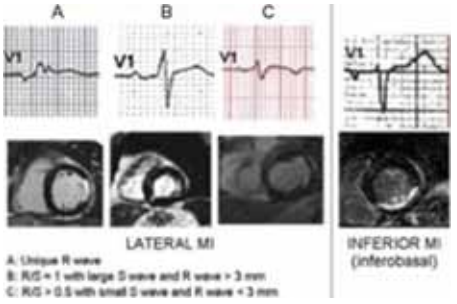
Purpose: The correct location of the necrosis in cases of Q wave MI, is important not only from the academic point of view but also for its clinical implications. Because of this, is necessary to clarify if the presence of prominent R wave in V1, as a mirror image of an infarction zone, is due to involvement of posterior wall or lateral wall.
Methods: In a total of 155 patients that has presented MI with infero-lateral zone involvement (Inferior, lateral and infero-lateral MI, proved by CE-CMR) the following ECG parameters were evaluated: R in V1 ≥3 mm, R/S ratio in V1 ≥1 (classic criteria for posterior MI), and R/S ratio in V1 ≥0.5 and correlated with MI location according CE-CMR
Results: R ≥3 mm criteria: Present in 30 cases: 5 cases of IM lateral, 23 cases of infero-lateral MI, 2 cases of inferior MI. Absent in 125 cases, 73 lateral/infero-lateral MI (26/47), 52 inferior MI. (SE 27.7%, SP 96.4%). R/S ≥1 criteria: Present in 20 cases: 3 cases of lateral MI, 17 cases of infero-lateral MI, 0 cases of inferior MI. Absent in 135 cases, 81 cases of lateral/infero-lateral MI (28/53), 54 cases of inferior MI (SE 19.8%, SP 100%). R/S ≥0.5 criteria: Present in 47 cases: 6 cases of lateral MI, 39 cases of infero-lateral MI, 2 cases of inferior MI. Absent in 108 cases, 56 cases of lateral/infero-lateral MI (25/31), 52 cases of inferior MI (SE 44.6%, SP 96.4%)



Lead V1 in lateral and inferior MI.

Conclusions: The criteria R ≥3 mm in V1 and R/S in V1 ≥1 are vary specific but with low sensitivity for diagnosis of lateral MI. The criteria R/S ≥0.5 has greater sensitivity with no significant reduction in specificity.
The prominent R wave in V1 according the exposed criteria (including the classic criteria for posterior MI), is due to lateral MI and not to involvement of infero-basal segment of inferior wall (old posterior wall)

P6370 | BEDSIDE

Cardiac sympathetic denervation is related with microvascular dysfunction in non-infarcted myocardium in patients with ischemic cardiomyopathy

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Purpose: Myocardial infarction (MI) results in sympathetic innervation injury of the scar and adjacent areas, which is associated with sudden cardiac death. Sympathetic denervation has also been observed in patients with chronic multivessel coronary artery disease but without MI, suggesting that perfusion abnormalities lead to sympathetic nerve injury. Impaired hyperemic myocardial blood flow (MBF), reflecting subtle perfusion abnormalities may therefore be associated with sympathetic nerve injury in non-infarcted myocardium. The aim of this study was to assess the relation of positron emission tomography (PET) assessed sympathetic innervation and hyperemic MBF in non-infarcted myocardium.

Methods: Patients with ischemic cardiomyopathy, referred for primary prevention implantable cardioverter defibrillator therapy according to current guidelines were included. [15O]H2O- and [11C]Hydroxyephedrine (HED)-PET was performed to quantify resting MBF, hyperemic MBF, and sympathetic innervation. Late gadolinium enhanced-cardiac magnetic resonance (LGE-CMR) imaging was performed to assess left ventricular end-systolic (LVESV) and end-diastolic volumes (LVEDV), and scar size. HED retention index (RI) and MBF were assessed in remote segments without scar, selected on LGE-CMR results.
Results: 44 patients were included (38 men, age 67±8 years, LVEF 29±6%). In non-infarcted myocardium, HED RI positively correlated with hyperemic MBF (R=0.45, p<0.01), resting MBF (R=0.31, p=0.04), and negatively with LVESV (R=-0.32, p=0.03) and LVEDV (R=-0.36, p=0.02). Multivariate linear regression analysis revealed that hyperemic MBF (B=0.68 p<0.01), LVEDV (B=-.005, p=0.01), and NTproBNP (B=-0.24, p=0.04) were independently associated with HED RI in remote myocardium.
Conclusion: Impaired sympathetic innervation is associated with impaired hyperemic MBF in non-infarcted myocardium in patients with ischemic cardiomyopathy. Whether impaired hyperemic MBF is the primary cause of this relation remains unclear.

P6371 | BEDSIDE
Characterization of coronary microvascular dysfunction in patients with suspected coronary artery disease

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Purpose: Coronary microvascular dysfunction (CMD) is defined as impaired myocardial perfusion in the absence of epicardial artery obstruction. This may cause chest pain, ECG abnormalities and stress perfusion results mimicking epicardial coronary artery disease (CAD). We evaluated CMD in symptomatic patients with intermediate probability of CAD with comprehensive anatomical and functional imaging tests.
Methods: We recruited prospectively 189 patients with intermediate pre-test probability of CAD. All patients underwent computed tomography coronary angiography (CTCA), quantitative positron emission tomography (PET) perfusion imaging with 15(O)-water during adenosine stress using a hybrid scanner, invasive coronary angiography (ICA) and fractional flow reserve (FFR) when feasible. CMD was defined as abnormal myocardial perfusion (stress MBF <2.5mL/g/min) and absence of haemodynamically significant CAD (<50% stenosis or FFR >0.8).
Results: Significant obstructive CAD was found in 38%, non-obstructive in 40%, whereas 22% had no coronary atherosclerosis. Stress myocardial perfusion abnormalities were present in 72 patients (38%). These were explained by matching epicardial stenosis in 55, whereas 17 patients (9.0%) had CMD. Of these, 2 had globally reduced stress perfusion without any coronary atherosclerosis. Four patients had globally reduced stress perfusion in the absence of haemodynamically significant CAD, but non-obstructive atherosclerosis on CTCA. Eleven patients, who had significant obstructive CAD, had additional perfusion abnormalities in regions unmatched with the obstructive lesions. Of CMD patients 24% were female, 41% had diabetes or prediabetes, 71% dyslipidemia, 47% hypertension, 65% family history of CAD and 17% were currently smoking. Type of chest pain was typical in 5 (29%) and atypical in 10 (59%) patients and 2 patients had other symptoms.
Conclusions: In a patient population with intermediate probability of CAD, some features of CMD can be identified in 9% of the patients who have numerous risk factors. However, CMD without any coronary atherosclerosis is rare (1%). Coexistence of CMD with non-obstructive CAD (3%) and obstructive CAD (6%) is more common. Quantitation of myocardial perfusion combined with anatomical imaging provides comprehensive way to identify CMD.

P6372 | BEDSIDE
Increased hsCRP in patients with acute-onset chest pain and significant coronary artery stenosis assessed with MDCT despite normal ECG and plasma troponines

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Purpose: Plasma high-sensitivity C-reactive protein (hsCRP) is significantly elevated in patients with acute coronary syndrome (ACS), whereas the potential clinical value of hsCRP in patients with acute-onset chest pain but without ACS has not been fully established. The aim of this study was to evaluate the correlation between hsCRP and the presence of significant coronary artery stenosis assessed with 320-slice multidetector computed tomography (320-MDCT) in patients with acute-onset chest pain and subsequent normal plasma troponines and ECG.
Methods: We measured hsCRP in 473 patients with acute-onset chest pain referred to the emergency department, who turned out to have normal levels of plasma troponines and no significant changes in the 12-lead electrocardiogram during a 24-hour observation period. Coronary calcium score and measurement of luminal obstruction were evaluated with 320-MDCT angiography by independent observers. A significant coronary artery stenosis was defined as a diameter stenosis ≥50%.
Results: A significant coronary artery stenosis was found by 320-MDCT in 99 (21%) of the patients. The remaining 374 patients constituted the control group. The patient group with significant coronary artery stenosis was older (median age 60 vs. 54 years, p<0.0001), a larger percentage was men (73% vs. 53%, p=0.0005), and the median coronary calcium score was considerably higher (304 vs. 27, p<0.0001) compared with the control group. In addition, hsCRP was significantly higher in patients with a significant coronary artery stenosis (2.2mg/L vs. 1.4mg/L compared with controls, p=0.003). In a multiple regression analysis including sex, age, smoking status, hypertension, hypercholesterolemia, presence of diabetes, family disposition and coronary calcium score, hsCRP was found to be an independent predictor of significant coronary artery disease (p=0.05).
Conclusion: In patients with acute-onset chest pain and subsequent normal plasma troponines and ECG, hsCRP is higher in patients with than in patients without significant coronary artery disease assessed with 320-MDCT.

FLOW IN THE CORONARY: WHAT DO YOU NEED MORE?

P6374 | BEDSIDE
Can intracoronary non ionic contrast medium Pd/Pa predict fractional flow reserve with intravenous or intracoronary adenosin?

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Introduction: Functional assessment of coronary artery stenosis is performed by measuring the fractional flow reserve (FFR) under hyperemic conditions (Adenosine). But the use of Adenosine have several limitations such as; high cost and adverse systemic effects. Recent studies have tried to find a correlation between different parameters (iFR, Baseline Pd/Pa) obtained without adenosine and FFR. Objective: We sougth to investigate the relationship and correlation between FFR and the Pd/Pa value obtained after the intracoronary infusión of non ionic contrast medium (Pd/Pa-CM) and if this parameter enhances diagnostic accuracy for FFR prediction compared to the resting baseline Pd/Pa measurement.
Methods: From February 2013 through September 2013 we conducted a multicenter study that prospectively included 328 consecutive pressure wire data sets from 261 patients presenting intermediate coronary artery lesions (30-70% by QCA estimation). Patient demographic and angiographic lesion data were collected. Resting baseline Pd/Pa, Pd/Pa-CM after coronary infusion of a 6 mL bolus of non ionic CM and FFR after continuous intravenous (iv) adenosine infusion (140 μg/kg/min) or after intracoronary (ic) adenosine infusion (≥360 mcg in the left system and ≥90 mcg in the right coronary artery), were measured following a standard protocol in all the centers.
Results: Resting baseline Pd/Pa value was 0.72 to 1.0 (0.93±0.04), Pd/Pa-CM was 0.68 to 1.0 (0.90±0.06) and FFR value after Adenosine iv or ic 0.55 to 1.0 (0.83±0.08). The ROC curves for resting baseline Pd/Pa and for Pd/Pa-CM, using a FFR ≤0.80 as the reference standard variable showed an AUC of 0.88 (95% CI=0.84-0.92, p<0.001) and 0.92 (95% CI=0.88-0.94, p<0.001) respectively. The optimal cutoff values of resting baseline Pd/Pa and Pd/Pa-CM for the prediction of FFR >0.80, were >0.96 and >0.90 respectively. These values were present in a 30.4% (n=100) and a 42.0% (n=138), of the total data sets. Scatter plots of resting baseline Pd/Pa and Pd/Pa-CM, showed a better correlation and agreement points, with Pd/Pa-CM than baseline Pd/Pa. Sensitivity and NPV of the Pd/Pa-CM>0.90 were consistently high in all the subgroup analysis.
Conclusion: The Pd/Pa-CM shows a good correlation with FFR in the intermediate lesions, even better than that with resting baseline Pd/Pa. The cutoff value of Pd/Pd-CM >0.90 has an excellent NPV and sensitivity for determining lesion significance allowing to avoid adenosine-FFR determination in almost half of patients. This excellent diagnostic performance is not affected by angiographic or methodological variables (adenosine iv or ic).

P6375 | BEDSIDE
Percutaneous coronary intervention immediately improves coronary microcirculation function

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Purpose: Percutaneous coronary intervention (PCI) changes the diastolic velocity pressure relationship (DVPR) of the coronary circulation, but little is known about its underlying mechanisms.
Methods: Twenty-five patients with angina pectoris who underwent PCI of the left coronary artery (anterior descending artery, 16; circumflex artery, 9) were en-

rolled. Coronary flow velocity and pressure were measured distal to the stenotic lesion using a dual pressure-flow sensor guidewire under adenosine triphosphate infusion. The instantaneous hyperemic diastolic velocity-pressure slope index (IHDVPS; interpreted as coronary conductance) and the extrapolated zero-flow pressure (Pzf; interpreted as back pressure) were obtained from DVPR plot. Wave intensity analysis was used to identify and quantify individual pressure and velocity waves. A consistent pattern of six predominating waves was identified, and all wave components were compared.

Results: Myocardial fractional flow reserve improved from 0.730±0.161 to 0.898±0.065 (P<0.001) after the procedure. Wave intensity analysis revealed that PCI changed DVPR and significantly increased the forward-traveling waves and backward-traveling suction wave (table).

	Pre-PCI	Post-PCI	P value
Diastolic velocity pressure relationship			
Pzf (mmHg)	21.3±15.2	30.7±19.8	0.006
IHDVPS (cm/s/mmHg)	3.24±2.70	2.12±1.07	0.022
Estimated wave speed (m/s)	24.0±18.9	10.3±4.4	0.001
Cumulative wave intensity ($\times 10^3$ W/m^2/s)			
Dominant forward-traveling compression wave	5.9±4.4	10.9±7.3	<0.001
Forward-traveling decompression wave	2.5±1.6	3.5±2.7	0.028
Late forward-traveling compression wave	0.8±0.9	1.8±1.6	0.017
Early backward-traveling compression wave	4.4±3.8	7.4±5.6	0.042
Late backward-traveling compression wave	2.7±2.7	3.1±3.5	0.581
Backward-traveling suction wave	8.1±3.8	12.4±7.9	0.010

Values are shown in mean ± SD.

Conclusions: Pzf was decreased and IHDVPS was elevated in patients with significant coronary stenosis. PCI raised the dominant forward-traveling waves due to relieving stenosis as well as the backward-traveling suction wave. PCI may immediately improve the coronary microcirculation suction function.

P6376 | BEDSIDE
Relevance of index of microcirculatory resistance on fractional flow reserve in intermediate coronary artery stenosis

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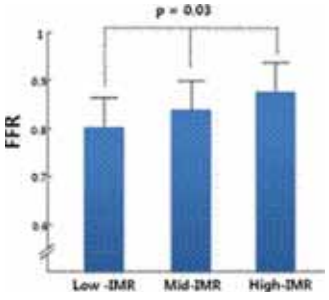
Purpose: We investigated the relevance of the index of microcirculatory resistance (IMR) and fractional flow reserve (FFR) of intermediate coronary lesion.

Methods: We enrolled patients who met the following criteria: stable angina with de novo coronary stenotic lesions of intermediate epicardial coronary stenosis (approximately 50–70% diameter stenosis) in the left anterior descending coronary artery. An intracoronary combined pressure-temperature sensor-tipped guidewire was used to measure the thermodilution-derived IMR and FFR.

Results: Sixty-seven intermediate coronary lesions (approximately 50–70% diameter stenosis) of the left anterior descending artery were analyzed in 67 patients. The IMR showed a modest correlation with FFR (r=0.31, p=0.01). However, no correlation between percent diameter stenosis and IMR was observed (r=0.12, p=0.35). Patients were divided into three groups, Low-IMR (n=22, IMR 14±3), Mid-IMR (n=23, IMR 21±2) and High IMR (n=22, IMR 36±10) according to the IMR value. In analysis of covariance, High-IMR group showed the significantly higher FFR value (0.87±0.07) than that in the Low-IMR group (0.81±0.08) (p=0.03, Figure 1). Lesions with FFR ≤0.8 were more frequent in the Low-IMR group (36%) than the Mid-IMR (22%) and High-IMR group (9%) (p=0.02).



Conclusions: Despite similar percent diameter stenosis and lesion length, intermediate coronary lesion with High IMR may reveal the significantly higher FFR compared with Mid and Low-IMR.

P6377 | BEDSIDE
The difference of the diagnostic efficacy of lumen area determined by optimal coherence tomography in the assessment of physiological coronary stenosis severity between LAD and RCA

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Background: Fractional flow reserve (FFR) has been established as the intracoronary physiology standard to evaluate functional relevance of coronary stenosis in the catheterization lab. The discordance between lesion severity determined by optimal coherence tomography (OCT) derived most stenotic lumen area and physiological significance derived from FFR was frequently observed. Impact of lesion locations on best cut-off values for FFR<0.80 has not been fully clarified. We further evaluated the significance of OCT-derived lesion characteristics for FFR assessment.

Methods and results: One hundred four discrete intermediate de novo coronary lesions from 100 SAP patients (73 lesions form LAD and 31 lesions from RCA) underwent quantitative coronary angiography, OCT and FFR assessments before coronary intervention, and were studied in the present study. Patients with acute coronary syndrome, old myocardial infarction or diffuse coronary narrowing were excluded. OCT-derived lesion characteristics including thin-cap fibroatheroma (TCFA) and plaque rupture (PR) were also evaluated. There was no significant difference in OCT minimal lumen area (MLA) size between LAD and RCA lesions (LAD: 1.46 (IQR 1.03-2.12) VS RCA: 1.44 (IQR 0.90-2.04); P=0.56), and FFR values were tended to be higher in RCA group (LAD: 0.74 (IQR 0.69-0.80) VS RCA: 0.80 (IQR 0.67-0.85); P=0.09). Regression analysis revealed that OCT MLA were associated with FFR in both LAD lesions and RCA lesions (LAD: R2=0.259, P<0.001, RCA: R2=0.446; P<0.0001). Receiver operating curve (ROC) analysis demonstrated the best cut-off value of OCT MLA in LAD lesions and RCA lesions were 1.52mm^2 and 1.18mm^2, respectively to predict FFR<0.80 (LAD: AUC 0.67; 95% CI: 0.55 to 0.77; P=0.022 VS RCA: AUC 0.88; 95% CI 0.71 to 0.97; P<0.001). Cut-off value was significantly smaller in RCA lesions and prediction efficacy was significantly better in RCA. Reverse functional mismatch (lesions with OCT MLA >1.9mm^2 and FFR <0.80) was more frequently observed in LAD lesions (LAD: 15 lesions (20.5%) VS RCA: 1 lesion (3.2%); P=0.013). Presence of TCFA was associated with lower FFR in RCA lesens, but not in LAD lesions. There was no significant association between PR and FFR both in LAD and RCA lesions.

Conclusion: Lesion location significantly affected OCT-derived morphological lesion severity assessment. Impact of lesion characteristics obtained by OCT may have an impact differently according to lesion locations.

P6378 | BEDSIDE
Fractional flow reserve for the prediction of cardiac events after drug-eluting stent implantation

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Background: Previous studies have identified post-stent fractional flow reserve (FFR) >0.90 as a useful surrogate for favorable long-term clinical outcome after bare-metal stent implantation. In drug-eluting stent (DES) era, anti-proliferative effect of DES have markedly reduced neointimal proliferation within stented segment and it is considered that the correlation between post-stent FFR and long-term outcome including target lesions revascularization (TLR) might be attenuated in lesions treated with DES. However, the prognostic value of post-stent FFR after DES implantation remains undetermined.

Methods: FFR measurements at maximum hyperemia were performed after elective percutaneous coronary intervention for coronary lesions treated with DES. Patients were followed up for at least one year. During one year follow-up period, TLR and major adverse cardiac events (MACE) were evaluated. MACE was defined as any death, myocardial infarction, stroke, or any revascularization.

Results: A total of 146 patients with DES implantation were enrolled. Pre interventional FFR increased from 0.68±0.09 to 0.86±0.07 after stent implantation (p<0.001). During one year follow-up after stent implantation, TLR and MACE occurred in 11 and 33 patients (7.5% and 22.6%). There was no significant difference in post-stent FFR between patients with or without subsequent TLR (0.87±0.05 vs. 0.86±0.07; p=0.67). After grading lesions to 3 categories according to the post-stent FFR (below 0.80, 0.81 to 0.90, and 0.91 to 1.00), there was no significant difference in the incidence of TLR and MACE among 3 categories (Fig. 1, 4.3%, 9.1% and 6.5%; p=0.72, 8.7%, 22.1% and 24.0%; p=0.30).

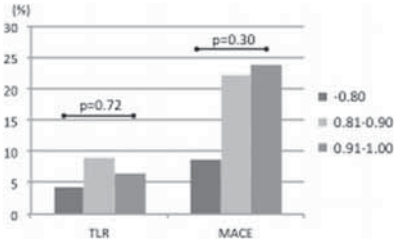

Figure 1. Adverse events at one year.

Conclusion: In patients treated with DES, post-stent FFR couldn't predict subsequent TLR or MACE at one year.

P6379 | BEDSIDE
Phasic coronary blood flow pattern and vasodilator reserve of the right ventricle

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Purpose: Coronary blood flow in the left ventricle has been extensively studied in health and disease. However, what little is known about right ventricular myocardial perfusion is from experimental animal studies. The purpose of our study was to assess phasic coronary blood flow pattern and flow reserve of the right ventricle.
Methods: Nine patients underwent coronary blood flow velocity measurements, using a 0.014 inches Doppler guidewire in the right ventricular branch (RVB) and in the right coronary artery (RCA) distal to the origin of RVB. Measurements were recorded at baseline (b) and at maximal hyperemia (h) after adenosine administration. Coronary flow reserve (CFR) was calculated as the ratio of the time-averaged peak coronary flow velocity (APV) at maximal hyperemia (h-APV) to the APV at baseline (b-APV).
Results: Results are shown in the table and the figure.

Table 1

	Diameter mm	b-APV cm/sec	b-DSVR	h-APV cm/sec	h-DSVR	CBF ml/sec	CFR
RCA	2.9±0.7	23.8±9.5	1.25±0.33	53.1±11.3	1.2±0.21	1.41±0.23	2.39±0.53
RVB	1.3±0.5	17.8±9.5	0.89±0.21	41.3±16.8	0.83±0.09	0.22±0.14	2.49±0.89
p	<0.05	<0.05	<0.05	NS	<0.05	<0.05	NS

DSVR: diastolic to systolic velocity ratio.

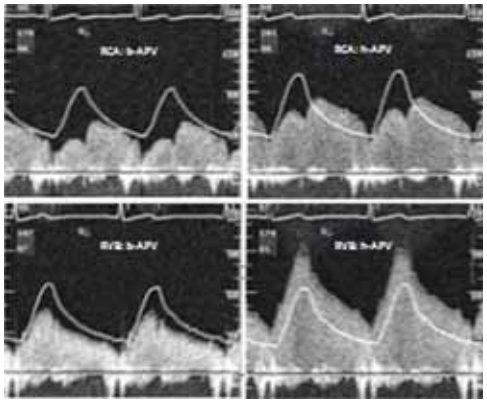

Figure 1

Conclusions: Coronary blood flow in the RV is out of phase with that in the left ventricular myocardium, showing a systolic predominant pattern. Although a small proportion of the right coronary blood flow is directed to the right ventricle, there was no significant difference in resting CFR between left and right ventricular myocardium.

P6380 | BEDSIDE
Impact of coronary plaque burden and composition on peri-procedural myocardial infarction and coronary flow reserve after percutaneous coronary intervention

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Background: Peri-procedural myocardial infarction (PMI) is one of the major complications of percutaneous coronary intervention (PCI). We investigated the influence of coronary plaque burden and characteristics on PMI using intravascular ultrasound (IVUS) with radiofrequency-based tissue characterization technology (iMAP).
Methods and results: The study population consisted of 33 consecutive patients with stable angina pectoris who underwent PCI. IVUS images were recorded before and after PCI for offline analysis, and coronary flow reserve (CFR) was measured after PCI. PMI was defined as a post-PCI cardiac troponin T elevation >5x 99th percentile of the upper reference limit (0.014 ng/ml). The overall plaque volume in patients with PMI (n=12) was significantly greater than that in patients without PMI (n=21) (240.4±106.0 mm^3 vs. 152.1±76.9 mm^3, p=0.0096). The iMAP-IVUS analysis demonstrated that the fibrotic, lipidic, and necrotic tissue volume within culprit lesions were also greater in patients with PMI than in patients without PMI (129.4±52.2 mm^3 vs. 94.6±40.8 mm^3, p=0.041; 26.8±10.5 mm^3 vs. 15.8±11.5 mm^3, p=0.011; and 81.3±48.4 mm^3 vs. 40.2±33.6 mm^3, p=0.0071, respectively). Multivariate logistic analysis demonstrated that necrotic tissue volume was the only independent predictor of PMI. Multiple regression analysis demonstrated that the post-PCI CFR values significantly correlated with overall plaque volume (R2=0.21, p=0.0099), and there were no correlations with the percent tissue burden of each plaque component.
Conclusions: The iMAP-IVUS analyses demonstrate that necrotic tissue volume is a potent predictor of PMI. Microcirculatory disturbance after PCI is significantly influenced by overall plaque volume, regardless of plaque compositions.

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Supplemental oxygen does not affect coronary physiologic indices measured during elective percutaneous coronary intervention

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Purpose: Supplemental oxygen is frequently used during coronary interventional procedures. Existing scientific data however, provide little support for routine use in normoxemic patients. In experimental studies, hyperoxemia has been associated with a reduction of coronary blood flow as well as an increase in coronary micovascular resistance, implying potential detrimental effects in patients with coronary artery disease. We studied the effects of supplemental oxygen on coronary physiologic indices such as fractional flow reserve (FFR), coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR), all dependent on maximum coronary flow and minimal coronary microvascular resistance.
Methods: In 18 patients (mean age 69 y.) with stable coronary artery disease and a 40-80% diameter stenosis in the proximal or mid part of a major coronary artery, intracoronary pressure- and thermodilution-derived flow indices were recorded using a pressure-temperature sensor-tipped guidewire at baseline and during maximum hyperemia induced by i.v. Infusion of adenosine (140μg/kg/min). Patients were then randomly assigned in a double-blind fashion to mask inhalation of either oxygen 6 l/min (group 1, n=9) or room air (group 2, n=9) for ten minutes followed by repeated measurements of FFR, CFR and IMR. Coronary wedge pressure was recorded during balloon inflation allowing correction for collateral flow. Statistical analysis was performed using repeated measures ANOVA.
Results: Baseline FFR, CFR and IMR were 0,79, 3,0 and 13 for group 1 and 0,73, 3,4 and 12 for group 2. No significant changes in the indices were seen after 10 minutes of mask inhalation (mean differences for FFR, CFR and IMR 0, -0,25 and 0,1 for group 1 and 0,01, 0,53 and 1,8 for group 2).

Coronary physiologic indices

	FFR		CFR		IMR	
	before	after	before	after	besfore	after
Oxygen	0,79±0,07	0,79±0,08	3,0±1,4	3,3±1,9	13±3,6	13±5,0
Air	0,73±0,17	0,72±0,16	3,4±1,9	3,8±2,1	12±5,6	14±6,4

Values are mean ± SD.

Conclusions: In patients undergoing elective percutaneous intervention supplemental oxygen did not significantly influence coronary physiologic indices. This may reflect that vasoconstrictive effects of hyperoxemia are outweighed by the endothelium-independent mechanisms mediating vasodilation during adenosine-induced hyperemia.

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Intermediate-term within-subject reproducibility of instantaneous wave-free ratio and its hemodynamic dependence in comparison with fractional flow reserve

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Background: The instantaneous wave-free ratio (iFR) is a novel pressure-derived index of coronary physiological stenosis severity without vasodilator drugs. Intermediate-term within-subject variability of iFR and its hemodynamic dependence or the relationship with microvascular resistance has not been fully investigated.
Methods and results: Fractional flow reserve (FFR), iFR, and the index of microcirculatory resistance (IMR) were measured twice, in 37 coronary arteries from 37 patients (65.8±9.6y) with an average interval of 43±22 days. Hemodynamic status including aortic pressure, distal coronary artery pressure, and heart rate were similar between the 2 measurements. There were no significant difference in iFR, FFR, and IMR between the 2 measurements (iFR: 0.88±0.08 vs 0.88±0.06, FFR: 0.77±0.06 vs 0.78±0.07, IMR: 21.7±10.4 vs 19.9±9.3, respectively). Regression analysis showed significant relationship between the 2 measurements for all three meausres (iFR:R2=0.69, p<0.001, FFR:R2=0.65, p<0.001, and IMR:R2=0.31, p<0.001, respectively). The repeatability coefficients and relative repeatability of coefficients of iFR, FFR, and IMR were 0.09 (10.2%), 0.08 (10.4%), and 18.2 (87.5%), respectively. Coefficients of variation of iFR, FFR, and IMR were 3.7%, 3.9%, and 31.8%, respectively. Reproducibility of iFR significantly correlated with heart rate (p=0.008). FFR and iFR showed a significant relationship (R2=0.46, P<0.001), whereas there was no association between FFR and IMR, nor between iFR and IMR.
Conclusion: iFR showed good reproducibility similar to FFR and independence of hyperemic microvascular resistance, although less independent of hemodynamic status.

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Lesion characteristics as a predictor of optimal post-stent fractional flow reserve

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Background: Previous studies have identified post-stent fractional flow reserve (FFR) >0.90 as a useful surrogate for favorable long-term clinical outcome after percutaneous coronary intervention. Higher value of post-stent FFR should be pursued for optimal percutaneous coronary intervention. However, there is little information regarding factors that influence post-stent FFR. The purpose of this study is to determine the impact of patient and lesion characteristics on post-stent FFR.
Methods: FFR measurements at maximum hyperemia were performed before and after elective percutaneous coronary intervention. Lesions with pre-interventional FFR >0.80, lesions with bypass graft and patients with acute myocardial infarction were excluded. If final value of FFR after stent implantation was >0.90, this post-stent FFR was considered as optimal post-stent FFR. For lesion characteristics, pressure drop pattern of FFR was assessed and classified into "abrupt pattern" and "gradual pattern" according to the pullback curve of FFR. The effect of patient and lesion characteristics including pressure drop pattern on post-stent FFR was evaluated.
Results: A total of 205 lesions with stent implantation were evaluated. Pre-interventional FFR increased from 0.67±0.10 to 0.87±0.07 after stent implantation ($p<0.0001$). Optimal post-stent FFR was attained in 75 lesions (36.6%). On logistic regression analysis, optimal post-stent FFR was positively correlated with abrupt pressure drop pattern (HR, 2.1; 95%CI, 1.1-4.2; p=0.03) and pre-stent FFR per 0.1 increase (HR, 1.5; 95%CI, 1.0-2.1; p=0.03), and negatively correlated with lesion location in left anterior descending artery (HR, 0.18; 95%CI, 0.08-0.39; $p<0.0001$).
Conclusion: Abrupt pressure drop pattern, pre-stent FFR and lesion location of left anterior descending artery were independent predictors of optimal post-stent fractional flow reserve. Utilization of such information might help to optimize percutaneous coronary intervention.

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Whole blood viscosity is an overlooked parameter in evaluation of Fractional Flow Reserve (FFR)

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Purpose: Although Fractional Flow Reserve (FFR) is considered as the gold standard tool for functional assessment of coronary artery stenosis, this prominent technique may have some limitations. As a pressure-dependent measurement, it may be affected from blood viscosity. Whole Blood Viscosity (WBV) can be computed with a validated equation only with hematocrit and total plasma protein concentration. In this study we aimed to evaluate the relationship between FFR and WBV.
Methods: We included 327 patients who were perfomed FFR after evaluating baseline coronary angiogram. According to the FFR cut-off value of 0.80, we divided the patients into two groups: 115 patients with critical stenosis as FFR(+) group (68.9% male, mean age 62.4±9.1) and 212 patients without critical stenosis as FFR(–) group (73.9% male, mean age 61.3±9.6). WBV was calculated for both low-shear rate (LSR) (0.5 sec-1) and high-shear rate (HSR) (208 sec-1) from hematocrit and total plasma protein concentration with using a validated formulation.
Results: The prevalence of baseline characteristics and CV drug usage were statistically similar in two groups. Gensini Score was higher in FFR(+) patients (41.2±24.3 vs 25.4±18.9, $p<0.001$). FFR(+) group had significantly higher WBV for both LSR (69.1±22.2 vs 62.1±21.6, p=0.006) and HSR (17.1±1.3 vs 16.7±1.1, $p<0.001$). Correlation analysis demonstrated a significant relationship between FFR value and WBV for LSR (β=-0.165, p=0.003) and HSR (β=-0.205, $p<0.001$). In multivariate logistic regression analysis, WBV at LSR (OR: 1.021, 95%CI: 1.009-1.033; p=0.001) and at HSR (OR: 1.037, 95%CI: 1.025-1.050; $p<0.001$) were independent predictors of critical stenosis in FFR.
Conclusion: In our study, we have delinated that WBV has an important assosiation with FFR values. While evaluating FFR results, WBV should not be overlooked.

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Considerations in the interpretation of myocardial single photon emission computed tomography for detection of myocardial ischemia using fractional flow reserve

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Background: Myocardial single photon emission computed tomography (SPECT) is an established noninvasive method for the assessment of the functional significance of coronary artery stenosis. However, myocardial SPECT was considered to have some limitations in patients with multi-vessel disease, acute myocardial infarction, non-culprit lesion. The aim of this study was to elucidate the consideration in the interpretation of myocardial SPECT for detection of myocardial ischemia by using fractional flow reserve (FFR).
Methods: We enrolled 124 patients (131 lesions) with significant coronary artery disease (CAD) who underwent myocardial SPECT followed by conventional coronary angiography (CAG) with FFR retrospectively. Significant CAD was defined as >50% diameter stenosis assessed by QCA. We compared the functional reserve of each epicardial vessel as detected by FFR and the perfusion defects in each myocardial territory as detected by myocardial SPECT in patients with multi-vessel disease, acute myocardial infarction and non-culprit lesion. Functionally significant stenosis was defined as FFR ≤0.8. Image analysis of myocardial SPECT was performed by two experienced cardiologists.
Results: In comparison with FFR, the sensitivity, specificity, negative and positive predictive value of myocardial SPECT being able to detect myocardial ischemia was 41%, 79%, 59% and 65%, respectively. The agreement between FFR and myocardial SPECT in the same territories was 61% in total (Kappa = 0.21). However, the agreement between FFR and myocardial SPECT was 65% in patients with non-myocardial infarction, 40% in patients with myocardial infarction, 79% in patients with single vessel disease, 51% in patients multi-vessel disease, 67% in culprit lesion, and 53% in non-culprit lesion, respectively.
Conclusions: There was poor concordance between myocardil SPECT and FFR for the evaluation of myocardial ischemia especially in patients with myocardial infarction, multi-vessel disease, and non-culprit lesion. These factors must be considered to evaluate the functional significance of coronary artery stenosis by using myocardial SPECT.

INVASIVE IMAGING OF CORONARY DISEASE

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Achievement of very low ldl-c level and plaque vulnerability at non-culprit plaques in patients with stable coronary artery disease: insights from frequency-domain optical coherence tomography analysi

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Purpose: Intensive lowering LDL-C with statins has been demonstrated to reduce cardiovascular events and slow plaque progression. While statin use has been also reported to favourably modify fibrous cap thickness, the association between achieved LDL-C level and fibrous cap thickness under statin therapy has not been fully elucidated. Also, the benefit of achieving a very low LDL-C level to fibrous cap thickness remains unknown. As frequency-domain optical coherence tomography (FD-OCT) enables us to evaluate plaque microstructures, we sought to investigate plaque morphologies in patients having low LDL-C level by using FD-OCT.
Methods: 293 non-culprit lipid plaques in 280 stable CAD patients treated with statin were evaluated by FD-OCT imaging in the entire of target vessel requiring percutaneous coronary intervention. These plaques were stratified into 4 groups according to attained LDL-C level (<1.3, 1.3-1.8, 1.8-2.6, <2.6mmol/l). Clinical characteristics and FD-OCT derived plaque microstructures were compared.
Results: 23.9% and 7.9% of study subjects achieved LDL-C <1.8mmol/l and <1.3mmol/l, respectively. Patients who achieved LDL-C <1.3 mmol/l were more likely to be older (p=0.02) and receive high-dose statin ($p<0.001$). FD-OCT imaging demonstrated that achieving lower LDL-C level was associated with thicker fibrous cap at non-culprit plaques ($p<0.001$). The thickest fibrous cap was observed in patients with LDL-C <1.3 mmol/l. After adjustment for differences in clinical characteristics, plaques in patients achieved LDL-C <1.3mmol/l continued to demonstrate the thickness of fibrous cap (p=0.001).

	LDL-C				p-value
	<1.3mmol/l (n=22)	1.3–1.8mmol/l (n=45)	1.8–2.6 mmol/l (n=99)	>2.6mmol/l (n=114)	
High-dose statin	91%	76%	57%	43%	<0.001
LDL-C (mmol/l)	1.0±0.1	1.5±0.1	2.1±0.2	3.4±0.6	<0.001
HDL-C (mmol/l)	1.1±0.3	1.2±0.3	1.1±0.3	1.2±0.4	0.62
Plaque-based analysis	(n=23)	(n=47)	(n=103)	(n=120)	
Fibrous cap thickness (μm)	149±59	105±56	92±48	90±43	<0.001
Fibrous cap thickness after adjusted (μm)	135±43	108±66	98±40	96±41	0.001

Conclusions: Achievement of stricter LDL-C goal was beneficial to the thickness of fibrous cap at non-culprit plaques. Our findings may support more favourable effect of achieving very low LDL-C level to stabilizing non-culprit plaques in patients with stable CAD.

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Area and morphological feature of jailed side-branch ostium after single stent crossover evaluated by serial follow-up of 3-dimensional optical coherence tomography

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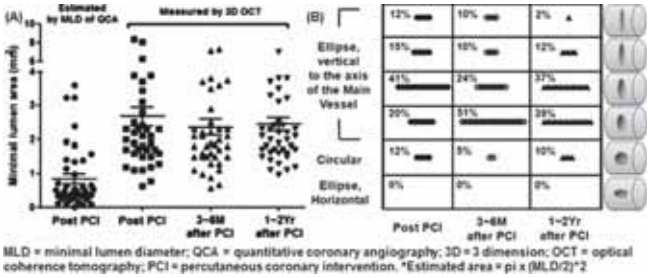
Purpose: This study evaluated area and shape of jailed side-branch ostium after single stent crossover using by serial 3 dimensional (3D) optical coherence tomography (OCT).
Methods: We enrolled 50 patients with single stent crossover at bifurcation lesions. All patients underwent three serial OCT follow-up (post, 3-6 months and 1-2 year after procedure). The inclusion criteria for jailed side-branch were ostial stenosis >50%, reference diameter ≥2mm, and Thrombolysis In Myocardial Infarction flow grade 3 by visual estimation. Total 9 patients were excluded due to poor OCT image quality. After 3D reconstructions of OCT data, we analyzed minimal lumen area (MLA) and shape of side-branch ostium.
Results: There was a significant correlation between the minimal lumen diameter (MLD) by quantitative coronary angiography (QCA) and minimal lumen area (MLA) by 3D OCT (r=0.73, p<0.001). But MLA estimated using MLD by QCA was much smaller than MLA measured by 3D OCT (0.84±0.14 vs. 2.66±0.27, p<0.001). There was no significant decrease of MLA during the follow-up (2.66±0.27 at post, 2.44±0.19 at 1-2 year after procedure, P=0.098). Shapes of side-branch ostium were almost vertical ellipse. Only about 10% of side-branch ostium had a circular shape and there was no horizontal ellipse shape.



MLD = minimal lumen diameter; QCA = quantitative coronary angiography; 3D = 3 dimension; OCT = optical coherence tomography; PCI = percutaneous coronary intervention. *Estimated area = pi x (MLD/2)^2
Figure 1. Area and shape of side-branch ostium.

Conclusions: Although MLD by QCA was significantly correlated with the MLA by 3D OCT, QCA overestimated the stenosis severity of side-branch after single stent crossover. There was no significant decrease of luminal area of side-branch during a study period. Shapes of side-branch ostium were almost vertical ellipse. This morphological aspect of side-branch ostium had to result in overestimation of the stenosis because of perpendicular x-ray projection on angiography.

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Long-term vascular response to biodegradable polymer biolimus-eluting stents in comparison with durable polymer sirolimus-eluting stents and bare-metal stents

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Purpose: Long-term vessel response after biodegradable polymer biolimus-eluting stents (BES) implantation remains unclear. We sought to evaluate the vascular response of biodegradable polymer BES at 5 years after stent implantation using optical coherence tomography (OCT) as compared with that of durable polymer sirolimus-eluting stents (SES) and bare-metal stents (BMS).
Methods: Five-year follow-up OCT was performed in 30 patients with 33 stents (10 with 12 BES; 10 with 11 SES; 10 with 10 BMS). Quantitative parameters and qualitative characteristics of the neointima were evaluated.
Results: A total of 5,178 struts (BES, n=2,056; SES, n=1,410; BMS, n=1,712) were analyzed. The percentage of uncovered struts was 0.7% of the BES group, which was significantly lower and higher than that of the SES and BMS groups (3.8% and 0.0%, P<0.001, respectively). Malapposed struts in the BES group were significantly lower than the SES group (0.2% vs. 2.4%, P<0.001), whereas they did not differ from the BMS group (0.2% vs. 0.0%, P=0.39). Cross-sectional qualitative analysis of neointimal tissue showed that the frequency of lipid-laden neointima was significantly lower in the BES group than the SES group (6.3% vs. 13.9%, P=0.031), and similar to the BMS group (6.3% vs. 5.2%, P=0.83).
Conclusions: Biodegradable polymer BES shows a favorable vascular response compared to SES, but slightly different response from BMS at 5 years follow-up. The observed frequency of in-stent neoatherosclerosis within BES is similar to BMS and significantly lower than SES, which may be due to the difference of polymer between BES and SES.

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Histopathologic validation of optical frequency domain imaging diagnosis of various coronary artery calcification

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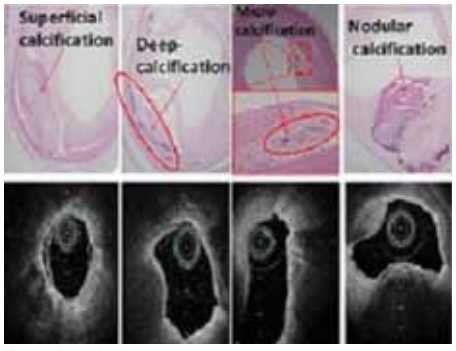
Background: Optical Frequency Domain Imaging (OFDI) is a novel, high resolution intravascular imaging modality. The aim of this study was to evaluate diagnostic accuracy of OFDI for the detection of coronary artery calcification as compared with histology.
Method: OFDI was performed in 478 pathological slices from 23 coronaries of 9 human cadavers. OFDI images were systematically co-registered to histological sections, beginning at the side branch segment with consideration of the distance along the longitudinal axis and pullback speed. Coronary calcification in each histological slice was classified as 4 types of calcification: superficial-dense-calcification, deep-calcification, microcalcification, and nodular calcification.
Result: Sixty-nine slices containing calcification were analyzed. It consisted of 35 superficial-dense-calcification (51%), 12 deep-calcification (17%), 21 microcalcification (30%) and 1 nodular calcification (2%).As shown in figure, superficial-dense-calcification was identified as low luminance, heterogeneous and clear border area by OFDI. Receiver-operating-characteristic-analysis identified calcium thickness <912μm as cut-points for measurable calcification (AUC=0.891).Also there was better agreement in measurable calcification thickness between OFDI and histological examination. However, all deep calcification were invisible on OFDI due to strong signal attenuation by coexisting necrotic-core. Microcalcification exhibited as low luminance, homogeneous and unclear border area like thin-cap fibroatheroma. Nodular calcification was identified as high-backscattering protrusions inside the lumen of the artery like red thrombus.



Types of calcification.

Conclusion: OFDI is useful to detect superficial-dense-calcification, however, careful diagnosis is necessary for other types of calcification.

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Des re-Endothelization for in-StEnt ResTenosis. The DESERT study

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Purpose: Incomplete struts coverage is a predictor of late stent thrombosis after drug eluting stent (DES) implantation in coronary atherosclerotic lesions. Struts coverage of DES implanted for bare-metal stent (BMS) restenosis has never been described.
Methods: Thirty-two patients with stable coronary artery disease, undergoing coronary angioplasty and treated with everolimus eluting stent implantation, were consecutively selected: eleven subjects with DES implantation to treat BMS restenosis were labeled as Group A whilst the remaining twenty-one patients who received a DES to treat de-novo lesions were labeled as Group B. In order to compare overlapping and non-overlapping struts, Group A struts were further divided in Group A1 (overlapped DES/BMS struts) and Group A2 (DES struts protruding outside the BMS edges). Coronary angiography was repeated with optical coherence tomography (OCT) evaluation at 6-month follow-up. The primary end-point of the study was the prevalence of uncovered struts evaluated by OCT analysis at six-month follow-up. Additional endpoints were the prevalence of cross-sections with at least one uncovered strut and the prevalence of cross sections with an uncovered strut ratio >0.3. These parameters were compared between Group A vs B and Group A1 vs A2.
Results: No differences were detected between the two groups in terms of age, gender and incidence of cardiovascular risk factors. Left anterior descending was the most frequently treated coronary artery in both groups of patients. In group A, vessel size, DES diameter and DES length were greater as compared to group B. A total of 85773 struts (17891 in group A and 67882 in group B) were analysed: as compared to group B, the percentage of uncovered stent struts was significantly lower in group A (2.6% vs 4.8%; P<0.0001) as well as the percentage of cross sections with at least one uncovered strut (13.5% vs 21.8%; P<0.0001) and the percentage of cross sections with uncovered struts ratio >0.3 (3.6% vs 7.9%;

P<0.0001). Comparison between Groups A1 and A2 revealed that DES struts protruding outside the BMS edges (A2) were more often uncovered (5.0% vs 1.9%; P<0.0001) and malapposed (4.1% vs 2.1%; P<0.0001) as compared to overlapped struts (A1).
Conclusions: This OCT study demonstrates that, at six-month follow-up, struts coverage is more complete in DES implanted for BMS restenosis as compared to DES deployed to treat atherosclerotic lesions, suggesting a lower risk of late stent thrombosis in the first group of patients.

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Prognostic impact of tissue protrusion after stenting in patients with acute coronary syndrome: an optical coherence tomography study

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Background: Optical Coherence Tomography (OCT) has been extensively studied in stent implantation to assess post-procedural results, with a view to optimizing outcomes. However, the real clinical impact of various OCT-defined abnormalities remains unknown. We investigated the prognostic impact of tissue protrusion between stent struts after stent implantation in patients with non-ST elevation acute coronary syndromes (NSTEACS).
Methods: Prospective study of consecutive pts with NSTEACS (≤72 h) undergoing PCI for an infarct-related artery presenting a single lesion without diffuse disease on the culprit artery. Patients were treated at the operator's discretion according to current guidelines. OCT was performed after initial coronary angiography and at the end of the angioplasty procedure. Tissue prolapse was defined as the projection of tissue (plaque or thrombus) into the lumen between stent struts after implantation. The primary endpoint of procedural complications associated no reflow, and PCI-related myocardial infarction (MI) as defined by a 20% rise in troponin over baseline levels at 24 hours according to the Universal Definition of MI 2012. Secondary endpoint was the functional result of angioplasty as assessed by fractional flow reserve (FFR) measured at the end of the procedure.
Results: 43 patients were included, mean age 63±11 ans, 90% were men. Tissue protrusion was observed in 35 (81%), with this tissue taking up a median 8.85% [IQR 6.2-14.2%] of the intra-stent area over a median length of 2.8mm [IQR 1.4-5.2]. Presence of tissue protrusion through the struts was not associated with cardiovascular risk factors or pre-treatment with aspirin, thienopyridines, antiGP IIb/IIIa or anticoagulants. Tissue protrusion had no impact on procedural complications or FFR (Table).

Tissue protrusion (% intra-stent area)

	1st quartile [0–6.2%]	2nd quartile [6.21–8.85%]	3rd quartile [8.86–14.15%]	4th quartile [14.16–31%]	p
No reflow	7.7%	22.2%	0	25%	0.33
Peri-procedural MI	6 (46%)	8 (80%)	6 (60%)	5 (50%)	0.39
FFR post stenting	0.94±0.03	0.94±0.06	0.93±0.03	0.93±0.04	0.99

FFR, fractional flow reserve.

Conclusion: Tissue protrusion through the struts after stent implantation is often observed by OCT in NSTEACS patients undergoing angioplasty and stenting. It occludes on average 10% of the intra-stent area, but does not seem to limit flow or have any impact on post-procedural complications.

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Pump flushing versus manual flushing for optimal optical coherence tomography imaging

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Purpose: Optimal blood clearance is a prerequisite for high image quality for optical coherence tomography (OCT). We investigated whether manual contrast flushing (MF) enables comparable image quality as pump flushing (PF).
Methods: We enrolled 25 consecutive patients, who underwent OCT imaging. Pullbacks were performed with both, MF and PF in a random order. Offline image analysis was performed frame-by-frame, blinded for the used method. Frames were categorized into three groups by the image quality: (1) insufficient, if residual blood caused any shadowing on the vessel wall, (2) acceptable, if no confluent blood was present but some blood speckles without compromise of the imaging at any part of the endothelial surface, or (3) perfect, if no residual blood was present.
Results: 84 pullbacks were analyzed, distributed equally between MF and PF groups. No difference was found in image quality, defined as the number of perfect or acceptable frames per pullback [246 (178; 262) vs 230 (192; 269) out the total of 272, respectively; p=0.989; Figure-A]. Comparing the methods on millimeter level, and defining quality as the worst frame of the given millimeter, we found no difference at any section of the total length either in perfect clearance (p=0.419) or in perfect and acceptable clearance (p=0.676). Amount of contrast used was significantly lower with MF compared to PF [12 mL (11; 13) versus 20 mL (17; 25), respectively; p<0.001; Figure-B]. Considering target vessel, lesion localization, vessel diameter and procedural phase, guiding size, flushing method, none of the anatomical or procedural factors were found to have an individual direct impact on image quality.

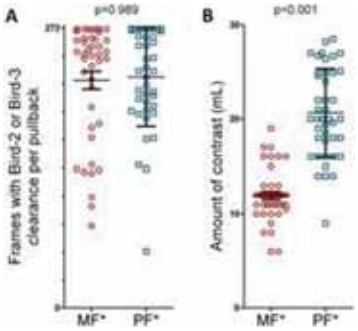

Image quality (A) and contrast use (B).
Conclusion: MF allows similar OCT image quality as PF, while needing markedly less contrast media.

P6394 | BEDSIDE
Incidence of acute coronary syndrome from in-stent neoatherosclerosis in patients with drug eluting stent evaluated by optical coherence tomography

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Objective: We investigate to clarify the role and frequency of neoatherosclerosis evaluated by optical coherence tomography (OCT) at long-term follow-up in patients with previous drug eluting stent (DES) implantation and acute coronary syndrome.
Methods and results: Forty-nine consecutive patients showed recurrent ischemia due to late phase (>6 month) restenosis of DES evaluated by coronary angiogram and OCT between August 2009 and August 2013 (18 with sirolimus eluting stents [SES], 12 with paclitaxel eluting stent [PES], 8 with zotarolimus eluting stent [ZES], and 11 with everolimus eluting stent [EES]). A lesion with features of Neoatherosclerosis (Lipid-laden intima, thin-cap fibroatheroma, thrombus, disrupted intima) was found in 15 stents with SES, 2 stents with PES, no stents with ZES, and 1 stent with EES (83.3%, 16.7%, 0%, and 9.1% respectively, p<0.05). Nine of 18 patients (50.0%) with features of neoatherosclerosis showed history of acute coronary syndrome (ACS). Furthermore, all of the patients who show ACS with neoatherosclerosis were treated by SES.
Conclusion: These results suggested that neoatherosclerosis might be possible mechanism for late phase occurrence of ACS in patients with DES, and frequency of neoatherosclerosis depends on the kind of DES.

P6395 | BEDSIDE
Impact of optical coherence tomography-versus intravascular ultrasound-guided percutaneous coronary intervention on mid-term clinical outcomes

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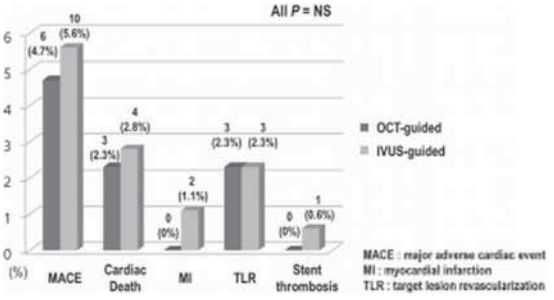
Background: Intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) can provide stent optimization and has impact on favorable clinical outcomes. Although optical coherence tomography (OCT) shows superior spatial resolution when compare to IVUS. The aim of this study was to evaluate whether OCT guided PCI can be a substitution for IVUS guided PCI in the real world population.
Methods: Patients treated with stent implantation under OCT or IVUS guidance were enrolled from an university medical center and an university hospital OCT and IVUS image databases. A total of 306 patients were included (129 with OCT guidance and 177 with IVUS guidance). Patients with left main disease were excluded. OCT and IVUS-guided PCI were defined as 1) a final minimum stent area ≥90% of the distal reference lumen area or MSA ≥5 mm^2 2) requiring additional



One year event between the two groups.

interventions based on the OCT or IVUS findings immediately after stent implantation. The primary endpoint was a cumulative incidence of major adverse cardiac events (MACE) including cardiac death, myocardial infarction (MI) and target lesion revascularization (TLR) at 1-year follow-up period. Definite or probable stent thrombosis (ST) rate was also evaluated.
Results: In the OCT-guided group, 11 of 129 patients (8.5%) received additional interventions whereas 23 of 177 patients (14.7%) were treated in the IVUS-guided group. The incidences of MACE rate between OCT-guided and IVUS-guided groups at 1-year follow-up was not different (4.7% vs. 5.6%, p=NS). ST was developed in 1 patient in IVUS-guided group, but not developed in OCT-guided group (p=NS).
Conclusions: OCT-guided PCI was comparable to IVUS-guided PCI in terms of MACE and ST rates, suggesting that OCT guidance may be an alternative strategy for stent optimization.

P6396 | BENCH
Usefulness of optical frequency domain imaging for vasa vasorum visualization in stented coronary arteries in pigs and humans

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Purpose: Vasa vasorum (VV), nutrient microvessels of the vessel wall, is known to develop in vascular diseases and after drug-eluting stent (DES) implantation and thus could be a therapeutic target of cardiovascular diseases. However, current imaging techniques are limited to clearly visualize VV. In the present study, we thus examined whether optical frequency-domain imaging (OFDI) with excellent resolution is useful for visualization of VV in pigs and humans.
Methods: Sirolimus-eluting (n=6), biolimus A9-eluting (n=6) and bare metal stents (n=6) were implanted into the left coronary arteries in pigs for 1 month. After euthanization, image acquisition of the stented vessels was performed using the OFDI system. Then, proximal and distal segments adjacent to stented segments were isolated and stained for Masson's trichrome and von-Willebrand factor (vWF) stainings. Correlation between VV area measured in the cross-sections of OFDI and the area of vWF staining was examined. OFDI was also performed at 6-12 months after DES implantation in patients with coronary artery disease (CAD) (n=6).
Results: OFDI clearly visualized micro-lumen structures in the adventitia of the segments adjacent to the stented segments (Fig. 1A), which were also stained for vWF and thus VV (Fig. 1B). Importantly, there was a significant positive correlation between VV area by OFDI and the area of vWF staining ($P<0.01$, n=36 sections). Furthermore, in CAD patients, OFDI also clearly visualized coronary adventitial VV at the segment adjacent to the stented segment after DES implantation (Fig. 1C).

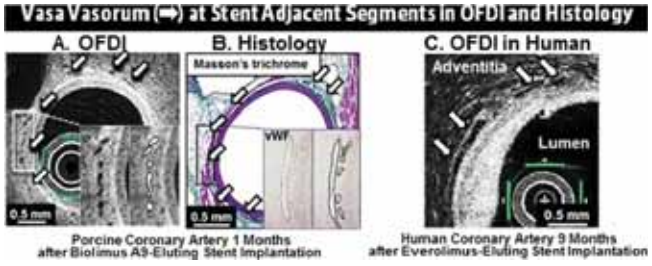

Figure 1. Vasa vasorum in OFDI and histology.

Conclusions: These results demonstrate for the first time that OFDI is useful for VV visualization, providing the tool to examine the role of VV in cardiovascular diseases.

P6397 | BEDSIDE
Serial OCT assessment of natural course of silent plaque rupture

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Background: Plaque rupture is one of the characteristics of vulnerable plaque responsible for acute coronary syndrome (ACS). Multiple plaque rupture of the non-culprit lesion could be occasionally detected by intravascular ultrasound or optical coherence tomography (OCT). However, the natural course of non-culprit-lesion ruptured plaque (NCRP) is unclear.
Purpose: The purpose of this study was to evaluate the frequency and natural course of NCRP.
Methods: Two hundred and five patients (67 ACS and 138 stable angina pectoris: SAP) who underwent percutaneous coronary intervention were analyzed. Ruptured plaque was defined as presence of a cavity that communicated with the lumen with an overlying residual fibrous cap fragment by OCT. Frequency and natural course of the non-significant, NCRP was evaluated by coronary angiography and OCT.
Results: OCT imaging was performed in all 3 coronary arteries in 75 of 205 patients (37%) and in culprit coronary artery only in 130 (63%) patients at baseline. A total of 21 NCRP were detected at baseline in 21 patients (10%). During follow-up (median, 328 days), no clinical event related to the NCRP was documented. Ten of 21 (48%) NCRP were evaluated by serial OCT examination and 8 (80%) NCRP had healed at follow-up. Lumen area excluding ruptured cavity did not change significantly (baseline: 6.4 ± 2.7 cm^2 to follow-up:6.3 ± 2.8 cm^2, p=0.479).
Conclusions: The majority of NCRP detected by OCT resolved at follow-up and was not associated with clinical event.

P6398 | BEDSIDE
Significance of micro-vessels within atherosclerotic coronary plaques: a color-coded intravascular ultrasound study

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Background and purpose: It has been documented that neovascularization in atherosclerotic plaques is associated with plaque vulnerability. This study was to examine tissue characteristics of plaque with micro-channels detected by optical coherence tomography (OCT). The tissue was assessed by use of a commercially available color-coded intravascular ultrasound (IVUS), iMap software.
Method: A total of 61 coronary plaques was classified into two groups: plaques with micro-channels (Pm, n=37) and without (Po, n=24). Micro-channel was defined as a tiny tubule with a diameter of 50 to 300 micrometers detected over 3 or more frames in OCT. Plaques over a length of 5mm were also analyzed by IVUS at the corresponded portion of the OCT imaging. The i-Map software identified four types of tissue component such asfibrotic, lipidic, necrotic, and calcified areas.
Result: There was no significant difference in plaque and vessel volume between the two groups. However, % content of fibrotic area was significantly smaller in group Pm than that in group Po ($68.33\%\pm11.25\%$ vs. $76.12\pm20.24\%$, p=0.039), while % content of necrotic area was significantly larger in group Pm than that in group Po ($13.44\%\pm5.79\%$ vs. $8.29\%\pm3.50\%$,p=0.022). There was no significant difference in lipidic and calcified areas between the two groups.
Conclusion: Plaques with micro-channels were more vulnerable than those without. These data suggested that micro-channels within coronary plaque might be related to plaque vulnerability.

IMPACT OF OPTICAL COHERENCE TOMOGRAPHY ON CORONARY MORPHOLOGY

P6400 | BEDSIDE
Impact of coronary calcification on different culprit lesion morphology in acute coronary syndrome

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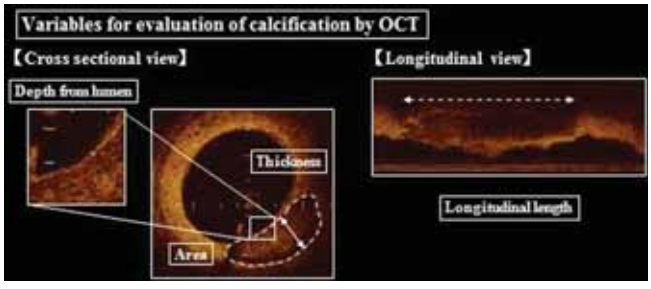
Background: Previous studies have reported plaque rupture and erosion were the most common causes of acute coronary syndrome (ACS) and spotty calcifications was identified as a marker of plaque rupture. Optical coherence tomography (OCT) offers a high-resolution imaging to assess the plaque morphology and coronary calcification.
Purpose: The aim of this study was to evaluate the relationship between the distribution of coronary calcification and the culprit lesion morphology in patients with ACS.
Methods: We enrolled consecutive 183 patients with ACS (mean age: 68 ± 11 years, 148 males). Culprit lesion was assessed by OCT and patients were divided into the rupture and non-rupture group according to the OCT findings. Maximum radial thickness, cross-sectional area of calcification and radial depth from the lumen and longitudinal length of calcification were compared between 2 groups.
Results: Plaque rupture was detected at culprit site in 105 patients and coronary calcification was identified in 58 patients. There were no significant differences in age and gender between 2 groups.
Maximum thickness, area and longitudinal length of calcification were smaller in rupture group (457.4 ± 284.9 μm vs. 722.1 ± 384.1 μm, $p<0.01$, 0.7 ± 0.4 mm^2 vs. 1.8 ± 1.4 mm^2, $p<0.01$, 2.2 ± 1.1 mm vs. 5.6 ± 5.3 mm, p- <0.01, respectively). Radial depth of calcification from the lumen was significantly geater in rupture group (150.0 ± 65.3 μm vs. 83.1 ± 63.3 μm, $p<0.01$).



Conclusions: Distribution of coronary calcification could be associated with morphological etiology of ACS.

P6401 | BEDSIDE
A novel method to assess coronary artery bifurcations by OCT: Cut-plane analysis for side-branch ostial assessment from a main vessel pullback

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Background: In the assessment of coronary bifurcations, evaluation of side branch (SB) ostia by an optical coherence tomography (OCT) pullback performed in the main branch (MB) could speed up lesion evaluation. Dedicated software that reconstructs the cross-sections perpendicular to the SB centerline could improve assessment of SB ostia. We aimed to validate a new method (cut plane analysis) for assessing the SB ostium from a MB OCT pullback.
Methods: Thirty-one sets of frequency-domain OCT pullbacks, obtained from 28 patients, from both the MB and the SB of a coronary artery bifurcation were analyzed. Measurements of the SB ostium from the SB pullback were used as a reference. Measurements of the SB ostium from the MB pullback were then performed by 1)conventional analysis and 2)cut plane analysis, and the measurement error for each analysis was estimated.
Results: Correlations of measurements of the SB ostium, acquired from the MB pullback in comparison to reference measurements acquired from the SB pullback, were higher with cut-plane analysis than with conventional analysis, albeit not reaching significance (area: Rcutplane=0.927 vs. Rconventional=0.870, p=0.256; mean diameter: Rcutplane=0.918 vs. Rconventional=0.788, p=0.056; minimum diameter: Rcutplane=0.841 vs. Rconventional=0.812, p=0.734; maximum diameter: Rcutplane=0.770 vs. Rconventional=0.635, p=0.316). Cut-plane analysis was associated with lower absolute error for SB ostium measurements than conventional analysis (area: 1.50±1.31mm^2 vs. 0.56±0.45mm^2, p<0.001; mean diameter: 0.44±0.30mm vs. 0.18±0.14mm, p<0.001; minimum diameter:0.39±0.29mm vs. 0.22±0.27mm, p=0.007; maximum diameter: 0.59±0.37mm vs. 0.30±0.26mm,p<0.001). Intra- and inter-observer agreement for cut plane analysis was high.
Conclusions: Area measurements of SB ostium performed by cut-plane analysis of an OCT pullback performed in the MB have high correlation with reference measurements performed from a SB OCT pullback and lower error compared to conventional analysis. This approach could alleviate the need for SB instrumentation and potentially reduce procedural complexity in assessment of coronary bifurcations.

P6402 | BEDSIDE
Relationship between thin-cap fibroatheroma and plaque progression in patients with coronary artery disease-an intravascular ultrasound and optical coherence tomography study-

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Background: Intensive lipid lowering therapy using statin has been reported to cause coronary artery plaque regression in patients with coronary artery disease (CAD). However, morphological characteristics of non-culprit coronary plaques that progress subsequently have not been elucidated. The aim of this study was to clarify the morphological characteristics of non-culprit coronary plaques in patients with CAD using intravascular ultrasound (IVUS) and optical coherence tomography (OCT).
Methods and results: A total of forty-nine CAD patients (acute coronary syndrome (ACS); n=38, non-ACS; n=11) undergoing percutaneous coronary intervention (PCI) were studied by both IVUS and OCT during acute phase, and IVUS examination at 10-month follow-up. Non-culprit 10mm segment with mild to moderate plaque in the target vessels at least 5mm proximal or distal to the stent edge were analyzed. Baseline characteristics of those plaques were evaluated by OCT and IVUS, and change of plaque volume between baseline and follow-up period was quantified by IVUS. Volumetric IVUS analysis was performed at 1mm intervals for each 10mm segment, and plaque progression/regression was evaluated. Patients were divided into 2 groups; progression group (n=11) and regression group (n=38). All patients received statin treatment during follow-up. Baseline low density lipoprotein cholesterol (LDL-C) (132±47 vs. 130±34mg/dl) and reduction of LDL-C during follow-up (-35±34 vs. -35±22%) were similar between the groups, whereas no IVUS parameters including plaque burden (p=0.11), plaque volume (p=0.35) and vessel volume (p=0.35) were correlated with plaque progression. Those with plaque progression showed a significantly higher incidence of thin-cap fibroatheroma (TCFA) (63 vs. 21%, p<0.01), and calcification (73 vs. 37%, p=0.04), compared with patients without plaque progression. Multivariate regression analysis showed that only TCFA (OR 9.82, p<0.05) was a predictor of plaque progression.
Conclusions: Non-culprit plaques with TCFA showed plaque progression as assessed by IVUS, indicating that intensive lipid lowering therapy and complete revascularization should be considered in patients with TCFA.

P6403 | BEDSIDE
Size discrepancy of frequency domain optical coherence tomography versus intravascular ultrasound in human coronary artery and phantom in vitro coronary model

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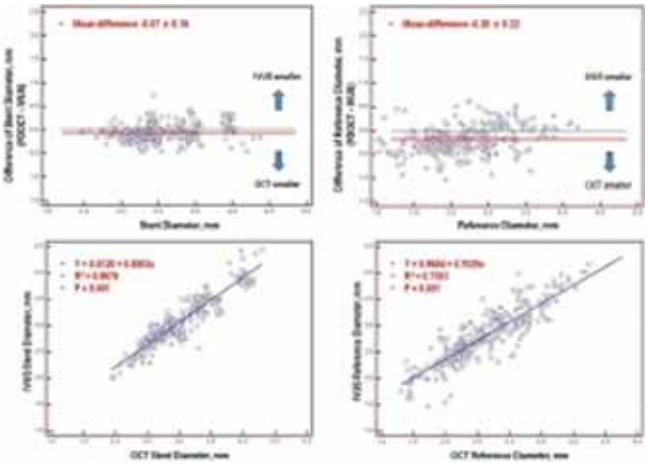
Background: In the real practice, frequency domain-optical coherence tomography (FD-OCT) is believed to depict smaller image than intravascular ultrasound (IVUS). But there are various results regarding their size discrepancy. The aim of the study was to compare the size discrepancy of FD-OCT and IVUS and investigate the mechanism of the size discrepancy.
Method: FD-OCT and IVUS were performed in a stent implanted phantom cylindrical coronary model and 57 stented human coronary arteries. Total of 11 matched FD-OCTand IVUS images from in-stent phantom model were measured. Meanwhile, total of 285 matched images at in-stent and distal reference segment from the 57 coronary lesions were measured in human coronary artery.
Result: In phantom model, FD-OCT showed similar lumen diameter as actual phantom diameter. IVUS overestimated lumen diameter by 5.9% (p<0.001) in reference segment and 2.5% (p<0.001) in stented segment. In human coronary artery, IVUS depicted larger diameter than FD-OCT in reference segment (2.57±0.60 mm vs. 2.77±0.49 mm, p<0.001) and in stented segment (2.99±0.49 mm vs. 3.05±0.45 mm, p=0.003). The difference of mean diameter was more prominent in reference segment (7.8%) than in stented segment (2.0%). Furthermore, correlation between FD-OCT and IVUS measurements were higher in stented segment than in reference segment (stented segment diameter R2=0.8670, reference segment diameter R2=0.7351; stented segment area R2=0.8663, reference segment area R2=0.7806).



Difference of stent reference diameter.

Conclusion: FD-OCT depicted smaller size than IVUS measurements in human coronary artery and the difference is more pronounced in non-stented segments than in stented segments. Pulsatile flow of human coronary artery and complex lumen morphology might be the reason of size discrepancy.

P6404 | BEDSIDE
Prediction of late neointimal regression after drug-eluting stent implantation by optical coherence tomography

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Background: Repeated intervention for mild to intermediate in-stent lesion after drug-eluting stent (DES) implantation may be safely deferred if late neointimal regression (LNR) could be predicted. Neointimal tissue characteristics may be related to late neointimal progression or regression late after DES implantation.
Purpose: The aim of this study was to predict LNR after DES implantation by optical coherence tomography (OCT).
Methods: Serial (12 and 18 months after DES implantation) OCT imaging was performed in 42 stented lesions from 26 patients. LNR was defined as [neointimal area (NIA) at 18 months - NIA at 12 months <0]. Clinical, lesion and OCT characteristics (both monphological and morphometrical) were compared between lesions with LNR and those without.
Results: LNR was observed in 24 of 42 (57%) lesions. Clinical, lesion and procedural characteristics were similar between lesions with and without LNR. By OCT, lesions with LNR had similar baseline neoinitmal area (2.2±1.5 vs. 2.2±1.5 mm^2, P=0.96). On the other hand, lesions with LNR had significantly higher prevalence of "homogenous" neointima (77 vs. 23%, P=0.0001) than those without LNR, where "heterogenous" neointima was the predominant neointimal tissue by OCT. "Homogenous" neoinitma was the only OCT predictor of LNR (P=0.004).
Conclusions: LNR was observed in about 60% of the mild to intermediate in-stent lesions. Presence of "homogenous" neointima may predict LNR.

P6405 | BEDSIDE

The association between tissue morphology assessed with optical coherence tomography and mid-term results after paclitaxel-coated balloon dilatation

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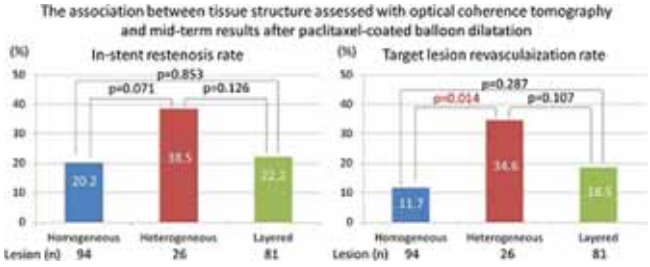
Purpose: The morphological assessment of neointimal tissue using optical coherence tomography (OCT) is highly significant to clarify the pathophysiology of in-stent restenosis (ISR) lesions. Mid-term results after paclitaxel-coated balloon (PCB) dilatation might differ depending on these OCT findings. The aim of this study was to define the impact of OCT findings on recurrence of ISR after PCB dilatation.
Methods: Between Octorber 2008 and August 2013, we performed PCI for 201 ISR lesions using PCB (161 men, mean age 68.4±9.8 years). The morphological assessment of neointimal tissue at the minimum lumen area site as to restenotic tissue structure (homogeneous, heterogeneous, or layered type) using OCT was performed. We examined the association between tissue structure and mid-term (6-8 months) results including ISR and target lesion revascularization (TLR) rates.
Results: The mean follow-up period was 195±36 days. The association of tissue structure with ISR and TLR rates is shown in the figure. The ISR rate of lesions with homogeneous structure tended to be lower than that with heterogeneous structure (20.2% vs. 38.5%, p=0.071), whereas the TLR rate of lesions with homogeneous structure was significantly lower than that with heterogeneous structure (11.7% vs. 34.6%, p=0.014).



Conclusions: The tissue morphology of ISR lesion assessed with OCT may have an impact on the mid-term efficacy of PCB.

P6406 | BEDSIDE

Serial FD-OCT assessment of complex calcified coronary plaque requiring rotational atherectomy

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Background: Target lesion calcification is known to influence the results of percutaneous coronary intervention (PCI). Rotational atherectomy (RA) plays an important role to facilitate the dilation or stenting of these lesions. The aim of this study was to assess the incidence of calcium crack after balloon angioplasty following RA and its impact on the results of PCI by serial FD-OCT evaluation.
Methods: From October 2011 to May 2013, a total of 21 calcified lesions requiring RA in patients with CAD were interrogated by FD-OCT. In all patients, serial OCT images just after RA, after balloon angioplasty, and after stent implantation were analyzed at 1-mm intervals. The arc, thickness of the calcium component, and the lumen area in each segment were measured after RA. Final Stent area and incidence of incomplete stent apposition (ISA) in each segment were analyzed. Lumen gain was calculated as: (final stent area) - (lumen area after RA). The incidence of calcium cracks after balloon angioplasty following RA was also assessed by OCT.
Results: A total of 398 segments in 21 lesions were analyzed. Calcium cracks after balloon angioplasty following RA and ISA after stent implantation were observed in 164 segments (41%) and 196 segments (49%), respectively. The segment with calcium cracks after angioplasty had smaller lumen area (3.73±1.66 vs 4.25±2.06 mm^2, $P<0.001$), larger calcium arc (290±78 vs 161±62 degree, $P<0.001$), and thinner calcium thickness (0.60±0.32 vs 1.05±0.42 mm, $P<0.001$) than those without cracks. The presence of calcium cracks after angioplasty was associated with larger lumen gain and fewer incidence of ISA after stent implantation (3.99±1.71 vs 3.28±1.61 mm^2, $P<0.01$, 40.5 vs 59.7%, $P<0.01$, respectively).
Conclusion: FD-OCT is effective for evaluating plaque characteristics in calcified coronary lesions. The presence of calcium cracks after rotational atherectomy and subsequent balloon angioplasty were the important manifestation to achieve optimal result after final stent implantation.

P6407 | BEDSIDE

Assessment of plaque calcification on optical coherence tomography and its relation with stent expansion after percutaneous coronary intervention

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Background: The presence of plaque calcification has been reported to be associated with inadequate stent expansion after percutaneous coronary intervention (PCI) that might affect the occurrence of long-term stent events such as stent thrombosis or restenosis in patients with coronary artery disease. However, the relationship between the extent of plaque calcification and stent expansion has not been fully investigated. We sought to assess the relationship between plaque calcification on optical coherence tomography (OCT) and stent outcomes after PCI.
Methods: We investigated 145 consecutive lesions in 145 patients with stable angina pectoris that underwent PCI with OCT examination. All lesions were treated with stent implantation (127 lesions with drug-eluting stents; 18 lesions with bare metal stents). Plaque morphologies including calcification arc and calcification thickness at the narrowest culprit sites on OCT were evaluated. After PCI, stent symmetry index defined as minimum/maximum stent diameter at the culprit site was calculated. The relationships between plaque morphologies and stent symmetry index were evaluated.
Results: The mean values of calcification arc and calcification thickness were 69.5±94.8 degrees and 275.7±344.5 μm, respectively. The lesions with asymmetrical stent expansion (symmetry index <0.70) (n=6) had larger calcification arc (171.2±105.1 degrees vs. 65.1±92.2 degrees, p=0.007) and greater calcification thickness (506.7±280.8 μm vs. 265.8±344.3 μm, p=0.09) than the lesions without. Stent symmetry index after PCI was negatively correlated with calcification arc (r = -0.20, p=0.01) and calcification thickness (r = -0.26, p=0.002) at the culprit sites. For predicting asymmetrical stent expansion, the cut-off values for calcification arc and thickness by receiver-operating characteristic (ROC) curve analysis were 145.5 degrees (area under the ROC curve (AUC): 0.778, p=0.007, sensitivity: 83.3%, specificity: 82.0%) and 400 μm (AUC: 0.701, p=0.03, sensitivity: 83.3%, specificity: 64.8%), respectively. The combination of large calcification arc (≥144.5 degrees) and great calcification thickness (≥400 μm) showed a high diagnostic capability to predict asymmetrical stent expansion as follows; sensitivity: 83.3%; specificity: 84.9%; positive predictive value: 19.2%; negative predictive value: 99.2%; and diagnostic accuracy: 84.8%.
Conclusions: Large calcification arc and great calcification thickness on OCT were related with post-procedural stent asymmetrical expansion, that might influence the long-term stent outcomes.

P6408 | BEDSIDE

Impact of the jailing configuration after bifurcational stenting on the side branch ostial stenosis at follow up

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Purpose: In a bifurcation intervention, single stent strategy was generally recommended and clinical benefit of final kissing balloon was controversial. The ostial stenosis of side branch (SB) jailed by main vessel stent has been seen at follow up. Three-dimensional optical coherence tomography (3D-OCT) is useful to assess the configuration of overhanging struts in front of SB orifice. It is unknown that an impact of jailing configuration on the lumen diameter of SB ostium without kissing balloon inflation (KBI). We compared the change of the SB ostial stenosis at follow up between two types of jailing configuration and the incidence of jailing configuration between 2-link (BES, biolimus eluting stent) and 3-link stents (EES, everolimus eluting stent).
Methods: Thirty-eight patients who underwent OCT examination after stent implantation at baseline (BL) were enrolled (BES 19 EES 19). 3D-OCT image reconstructions were done using the off-line workstation. The cases were divided into two groups according to the following classification of jailing configuration: 1)Free carina type (FC): there is no longitudinal link bridging from the carina, 2)Connecting carina type (CC): there is a longitudinal link connecting to the carina. According to the stent design, we compared the proportion of jailing configuration and the number of compartments divided by the jailing strut was counted. Moreover, 17 patients underwent OCT at follow up (FU). The changes of SB diameter were compared between FC and CC group.
Results: A total of 62 SB were identified. The configuration of overhanging struts could be evaluated in 55/62 (88.7%) SB on 3D-OCT (BES 26 EES29). In EES, FC was 16 (55.2%), CC was 13 (44.8%).In BES, FC was 17 (65.4%), CC was 9 (34.6%). The proportion of CC were similar between both groups (p=0.440). 29/55 (FC 17, CC 12) SB were evaluated at follow up. In both groups, the diameter of SB ostium decreased significantly (FC: BL 1.60±0.53mm FU 1.47±0.54mm, p=0.024, CC: BL 1.46±0.62mm FU 1.12±0.47mm, p=0.001). The percent reduction of SB diameter was significantly higher in CC than FC (CC: 23.4±10.7% FC: 5.9±17.2%, p=0.04). In CC group, the number of compartment was significantly greater than FC group (CC 2.50±0.67, FC 1.88±0.78, p=0.035). 3D-OCT demonstrated that small compartments were filled with tissue.

Conclusions: 3D-OCT could evaluate the configuration of overhanging struts in front of side branch orifice. The ostial diameter was decreased in the SB jailed by main vessel stent without KBI. The jailing configuration and compartment could affect the reduction of SB ostial diameter due to tissue attachment.

P6409 | BEDSIDE
Difference of vessel healings between Sirolimus- and Everolimus-eluting stent implantation in bifurcation lesions: from J-REVERSE OCT Sub-study

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Purpose: We aimed to clarify the differences of vessel healings after stenting in the bifurcation lesions between those treated with sirolimus-eluting stent (SES) or everolimus-eluting stent (EES).
Methods: J-REVERSE is a prospective multicenter registry of cases treated with provisional stenting to bifurcation lesions using SES (n=18) and EES (n=46) with or without final kissing inflation (FKI). The first 64 lesions at selected study sites were predefined for inclusion in the optical coherence tomography (OCT) sub-study and underwent 9-month follow-up OCT. In addition to standard OCT parameters, stent eccentricity index (SEI; minimum divided by maximum stent diameter), neointimal unevenness score (NUS: maximum neointimal thickness in the cross-section (CS) divided by the average NIT of the same CS: to assess the uniformity of neointima suppression), and the frequency of uncovered and malapposed struts were averaged for each segment (proximal, bifurcation, and distal segment).
Results: The rate of patients treated with FKI were similar between EES and SES (p=0.39). Overall, the average stent and lumen area, average NIT, and the frequency of uncovered strut were similar. Although EES tended to have smaller SEI than SES, the frequency of malapposed struts and average NUS in EES group were smaller than those in SES group, indicating more uniform vessel healing observed in EES. In the detailed segmental analysis, the disparities of the frequency of malapposed struts and SEI were observed in all the segment with a statistical significance in bifurcation segment. EES had significantly smaller NUS in the entire segment (Table 1).

Table 1

	EES (n=46)	SES (n=18)	P
Average NUS (over all)	2.0±0.3	2.3±0.5	0.006
Average NUS (proximal segment)	2.4±0.6	2.9±0.9	0.01
Average NUS (distal segment)	2.1±0.6	2.9±1.9	0.01
Average SEI (over all)	0.86±0.05	0.88±0.03	0.08
Average SEI (proximal segment)	0.86±0.06	0.87±0.04	0.40
Average SEI (bifurcation segment)	0.85±0.07	0.88±0.05	0.05
Average SEI (distal segment)	0.88±0.04	0.90±0.04	0.24
% malapposed struts, (%) (over all)	0.2±0.6	1.3±2.8	0.01
% malapposed struts, (%) (proximal segment)	0.63±1.7	1.1±2.4	0.44
% malapposed struts, (%) (bifurcation segment)	0	3.0±6.8	0.01
% malapposed struts, (%) (distal segment)	0	0	–

OCT analysis, NUS: neointimal unevenness score (maximum/average neointimal thickness), SEI: stent eccentric index (minimum/maximum stent diameter).

Conclusion: A prospective multicenter J-REVERSE registry demonstrated that, in the treatment of bifurcation lesions, EES offered homogeneous vessel healing with less malapposition probably due to tailored stent expansion to lesion morphology afforded by thin-strut platform.

P6410 | BEDSIDE
Impact of coronary artery stent edge dissections on long-term clinical outcome in patients with acute coronary syndrome- an optical coherence tomography study

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Purpose: The aim of this study was to assess the incidence, predictors and long term prognosis of edge dissections identified by optical coherence tomography (OCT) after the implantation of bare metal (BMS) and drug eluting stents (DES).
Methods: We studied 74 patients who underwent percutaneous coronary intervention (PCI) in a native coronary artery with BMS or DES because of an acute coronary syndrome.
Results: The OCT images of 74 vessels and 82 stents (38 BMS and 44 DES) were analyzed. Stent edge dissections were found in 29 of 74 patients (39,1%) (Fig. 1). Independent predictors of stent edge dissections were found to be the presence of ST-elevation myocardial infarction (STEMI) (p=0,002, odds ratio 0,13; 95% CI 0,03-0,47), the small reference lumen diameter (p=0,006, odds ratio 0,10; 95% CI 0,02-0,53) and the short stents implanted (p=0,011, odds ratio 0,85; 95% CI 0,76-0,96). During a follow-up period of 25,6±9,4 months 11 patients presented with at least one major adverse cardiac event. Event free survival was significantly decreased in patient with stent edge dissection with a flap thickness more than 0,31mm compared to patients with thinner flap or without any edge dissection (p<0,001).

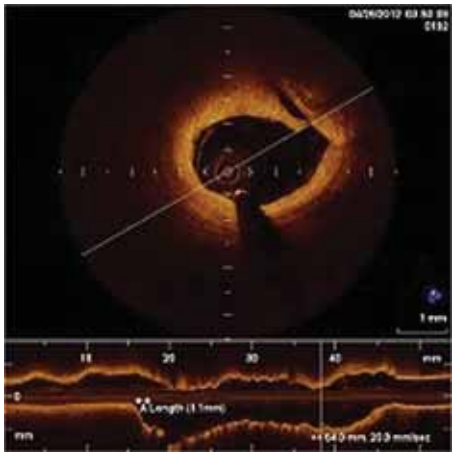

Figure 1

Conclusions: OCT frequently detects stent edge dissections, usually related to STEMI presentation and to PCI technique. Deep vessel wall injury at stent edges with a dissection flap thickness more than 0,31mm carries an adverse clinical impact on long-term clinical outcome.

P6411 | BEDSIDE
Impact of underneath plaque characteristics on the fate of acute incomplete strut apposition: serial optical coherence tomography sub-study of japan-drug eluting stents evaluation; a randomized trial

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Background: Little is known about the impacts of plaque characteristics on vascular response to incomplete strut apposition observed immediately after stent placement (acute ISA).
Methods: In the Japan-Drug Eluting Stents Evaluation; a Randomized Trial (J-DESsERT), 42 patients (47 stents) treated with either sirolimus (SES) or paclitaxel (PES) eluting coronary stent underwent serial OCT examination before and after implantation and at 8-month follow-up. Acute ISA were surveyed from OCT cross-sections post stenting and sum of acute ISA area was measured as well as plaque characteristics underneath acute ISA were assessed from matched OCT cross section before stenting. The fate of acute ISA was evaluated at 8-month.
Results: A total of 241 cross-sections with acute ISA were identified. Among those, 216 cross-sections (89.6%) were resolved- and 25 (10.4%) were persistent ISA. The mean ISA area of resolved ISA was significantly smaller than that of persistent ISA (0.25±0.20 mm^2 vs. 0.39±0.33 mm^2, p=0.048). Based on receiver operating curve analysis, the best cutoff value of acute ISA area for predicting resolved ISA was 0.175 mm^2 (sensitivity; 46.3%, specificity; 84.0%, AUC=0.659). Acute ISA over fibrous plaque resolved more frequently than those over lipid or calcified plaque (Ratio of ISA resolution; 95.1% over fibrous, 78.9% over lipid, 75% over calcified, p<0.001). Multivariate logistic analysis revealed fibrous plaque over acute ISA was the independent predictable factor associated with resolved ISA (OR: 7.582; 95% CI: 2.882 to 19.944; p<0.001). Late-acquired ISA was identified 18 cross-sections at 8-month follow-up. Among those, lipid plaque underneath late-acquired ISA was more frequently observed than fibrous or calcified plaque (77.8% on lipid, 16.7% on fibrous, 5.5% on calcified).
Conclusions: Plaque character underneath ISA as well as ISA area affect the fate of acute ISA after SES / PES implantation.

CORONARY IMAGING AND CLINICAL OUTCOME

P6413 | BEDSIDE
Vessel shrinkage (negative remodeling) is the main mechanism of lumen compromise in allograft vasculopathy. A long-term serial intravascular ultrasound study

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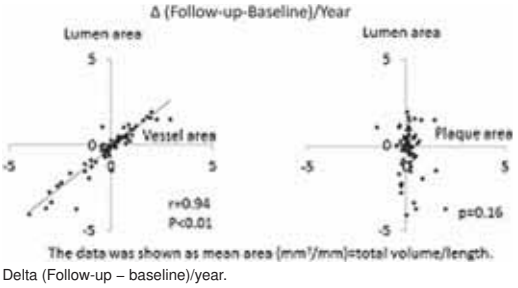
Purpose: There is limited long-term data on the mechanism of lumen compromise in cardiac allograft vasculopathy (CAV).
Methods: We performed serial intravascular ultrasound (IVUS) evaluation of the LAD in 66 consecutive heart transplant recipients. Baseline and follow-up (mean duration=3.2 years) proximal LAD segments were matched; and a ≥20mm long proximal segment was analyzed every 1mm, and results normalized for analysis length and reported as mm^3/mm.
Results: Overall, the change of mean lumen area was well correlated to the change in mean vessel area (r=0.94, p<0.01), but not to the change in mean plaque area (p=0.16) (Figure). Twenty two pts (33.3%) had a history of cellular rejection. Clinical characteristics, baseline IVUS, and follow up IVUS were similar between pts with vs without rejection. During follow up, vessel area decreased in pts with and without rejection (-0.25±1.62 vs -0.08±1.17 mm^3/mm, p=0.62). And plaque area increased in both groups (0.27±0.68 vs 0.09±0.33 mm^3/mm, p=0.16). As a result, lumen area decreased in both groups, and there was no significant difference between them (-0.53±1.67 vs -0.16±1.12 mm^3/mm, p=0.3). Furthermore, the correlations between mean lumen areas vs mean vessel or plaque areas were similar in pts with or without rejection.



Delta (Follow-up – baseline)/year.

Conclusions: Lumen loss occurs in long term follow up of CAV pts with and without rejection. Although plaque increase contributes to lumen loss, the main mechanism is vessel negative remodeling.

P6414 | BEDSIDE
Longitudinal stent deformation in the drug-eluting stent era: an intravascular ultrasound study

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Background: Longitudinal stent deformation (LSD) in drug-eluting stents (DES) has been described as a disruption of stent structure. We aimed to assess the degree and rate of LAD via intravascular ultrasound (IVUS) across different DES platforms.
Methods: Patients with implanted DES for de novo lesions were divided into 5 groups according to sirolimus-(SES); paclitaxel- (PES); zotarolimus- (ZES); cobalt- chormium everolimus (CoCr-EES); and platinum-chromium everolimus-eluting stents (PtCr-EES). Stent length was measured using automatic pullback of an IVUS catheter, and was compared to labeled length for calculation of absolute value of difference in length and relative difference (absolute value of difference divided by the labeled length).
Results: A total of 534 DES's in 475 patients were included. The baseline characteristics were comparable between groups; highest calcification as seen in the SES group (p=0.03). The absolute and relative absolute value of difference in length showed the lowest degree in the SES group and the highest in the ZES group (p=0.05 and 0.05, respectively). The absolute relative difference of >5% was lowest in the SES group compared to the other groups (p-0.009), however, significant (>15%) absolute relative difference was similar among groups (p=0.97) (Table 1).
Conclusions: LSD was seen in all stent platforms. However, the degree of LSD was lowest in the SES group. Incidence of significant LSD was low, with no significant difference see among al stent platforms.

P6415 | BEDSIDE
VH-IVUS analysis of attenuated plaque and ulcerated plaque and the relation between the plaque composition and slow flow/no reflow phenomenon during PCI

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Background: The attenuated and ulcerated plaques are thought as embolic prone plaque, however the plaque characteristics are unclear. This study aimed to assess the plaque characteristics of attenuated and ulcerated plaques in VH-IVUS and the incidence of slow flow/no reflow during PCI.
Methods: Subjects were 119 patients 121 lesions undergoing VH-IVUS before stenting. These lesions were divided into the 15 lesions with attenuated plaque, 24 lesions with ulcerated plaque, and 82 lesions without attenuated and ulcerated plaque (the control group).
Results: Results were shown in table. Of the ulceration group, the necrotic core area of acute coronary syndrome was significantly larger than the stable angina pectoris (3.0±1.4 mm^2 vs. 1.8±1.0 mm^2, p<0.05).

VH of Attenuation and Ulcerated plaque

	Attenuation group (n=15)	Ulceration group (n=24)	Control group (n=82)	p value
Acute coronary syndrome	9 (60%)	14 (58%)	42 (51%)	n.s.
Reference vessel diameter (mm)	3.07±0.58	3.41±0.58	3.15±0.51	n.s.* <0.05**
The incidence of slow flow/no reflow after stenting	3 (20.0%)	5 (20.8%)	4 (4.9%)	<0.05* <0.05**
Grayscale IVUS characteristics				
Lumen CSA (mm^2)	5.0±1.3	7.6±3.0	4.7±1.4	n.s.* <0.01**
EEM CSA (mm^2)	17.1±3.5	19.7±4.9	16.0±4.5	n.s.* <0.01**
Plaque and Media CSA (mm^2)	12.1±3.9	12.0±3.2	11.4±3.6	n.s.* n.s.**
VH-IVUS characteristics				
Fibrous (%)	55.7±9.5	56.9±10.0	61.7±9.9	<0.05* <0.05**
Fibro-fatty (%)	27.5±9.5	10.4±5.8	13.9±8.2	<0.01* <0.05**
Necrotic core (%)	12.2±6.1	20.7±9.0	15.9±9.0	n.s.* <0.05**
Dense calcium (%)	4.6±3.0	12.3±6.4	8.3±7.1	n.s.* <0.05**
Fibrous (mm^2)	6.8±2.6	6.8±2.2	7.1±2.8	n.s.* n.s.**
Fibro-fatty (mm^2)	3.5±1.9	1.2±0.7	1.6±1.2	<0.01* n.s.**
Necrotic core (mm^2)	1.3±0.4	2.5±1.3	1.7±1.0	n.s.* <0.01**
Dense calcium (mm^2)	0.5±0.4	1.4±0.7	0.9±0.8	n.s.* <0.01**

Conclusion: The attenuated plaque had significantly larger fibro-fatty tissue. The ulcerated plaque had significantly larger EEM CSA. The ulcerated plaque had significantly larger necrotic core and dense calcium. The ulcerated plaque in ACS had significantly larger necrotic core. The attenuated plaque and the ulcerated plaque showed higher frequency of slow flow/no reflow during PCI.

P6416 | BEDSIDE
The variable profile of endothelial shear stress and remodeling along the length of plaque determines the topography and natural history of coronary artery disease

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Purpose: Low endothelial shear stress (ESS) promotes atherosclerosis and expansive remodeling, leading to adverse vascular outcomes. However, the pattern of plaque progression in the longitudinal arterial axis and the corresponding pathobiologic mechanisms are not known. In this study, we assessed the hypothesis that the longitudinal variation of ESS and remodeling in plaque regions determine the topography and the natural history of coronary artery disease.
Methods: In the PREDICTION Study, we performed 3D coronary reconstruction by angiography/IVUS at baseline (BL) and at 6-10 months follow-up (FU). All discrete BL plaques (max thickness >0.5mm, length 9-30mm) were categorized as proximal, mid and distal 3mm-long segments. In these segments, we assessed BL remodeling index (RI) and ESS with computational fluid dynamics. At FU, we evaluated the plaque burden (PB) and lumen area change in the same locations.
Results: In 313 arteries from 220 patients, 371 plaques (length 16.6±0.4 mm) were identified. BL PB was higher in the mid plaque (45.8%) than in the proximal (43.8%) and distal plaque (43.5%, p<0.001). BL ESS was higher in the mid plaque (1.8 Pa) than in the proximal (1.7 Pa) and distal plaque (1.6 Pa, p<0.05). Remodeling was also non-uniform, as expansive remodeling was more frequent in proximal plaque (OR 1.7, 95%CI 1.3 to 2.3, p<0.001) and constrictive remodeling in mid plaque (OR 1.6, 95%CI 1.2 to 2.2, p<0.001). At FU, plaque regression was evident in all plaque portions (PB change -0.3% in proximal, -1.2% in mid,

Abstract P6414 – Table 1. The degree and rate of LAD through IVUS

	SES (n=112)	PES (n=108)	ZES (n=112)	CoCr-EES (n=109)	PtCr-EES (n=93)	p value
Absolute value of difference in length [IVUS-measured length-labeled length] (mm)	0.9±0.7	1.1±0.9	1.3±0.9	1.0±0.8	1.0±0.8	0.05
Absolute value of relative change in length [(IVUS-measured length-labeled length)/labeled length] (mm)	5.1±4.5	6.0±4.8	7.3±4.6	5.9±4.3	6.5±6.0	0.05
Absolute relative difference of >5%, n (%)	41 (36.6)	57 (52.8)	66 (58.9)	61 (56.0)	48 (53.3)	0.009
Absolute relative difference of > 15% (significant difference), n (%)	5 (4.5)	5 (4.6)	7 (6.3)	5 (4.6)	5 (5.6)	0.97

-0.9% in distal plaque, p=ns). Lumen area however increased only in the proximal and mid part while it decreased in the distal part of plaque (change 1.4%, 0.3% and -0.4% respectively, $p<0.05$). In the distal plaque region, 7% of segments exhibited a combination of low ESS and expansive remodeling at BL and both BL low ESS and expansive remodeling were independent predictors of lumen area narrowing at FU (beta -1.5mm^2/Pa, 95%CI -2.1 to -0.9, $p<0.001$ and beta -2.6 mm^2/unit increase in RI, 95%CI -3.2 to -2.1, $p<0.001$ respectively).
Conclusions: Plaque, arterial remodeling and ESS are heterogeneously distributed along the length of individual coronary plaques. Despite universal plaque regression in this aggressively treated patient population, the distal part of lesions manifests progressive luminal narrowing, under the synergistic local effects of low ESS and expansive remodeling. The detailed characterization of remodeling and ESS profiles along the longitudinal aspect of lesions may enhance the early identification of plaques at highest risk for adverse outcomes.

P6417 | BENCH
High-resolution intravascular ultrasound using optical coherence tomography technique: basic study

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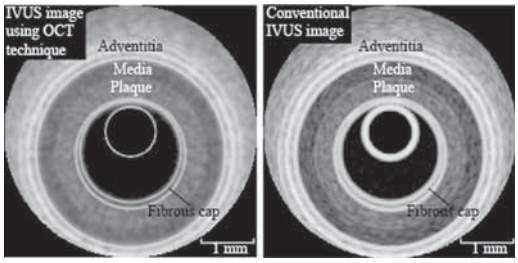
Purpose: Intravascular ultrasound (IVUS) provides visualization of the arterial wall with high penetration for the diagnosis of atherosclerosis. However, IVUS has an insufficient axial-resolution to measure the fibrous-cap thickness, and the assessment of the microstructure of the arterial surface requires the employment of optical coherence tomography (OCT). In this study, we applied the OCT technique to IVUS data to improve the axial-resolution of the IVUS image.
Methods: The OCT technique transforms the received signal in the time domain to that in the frequency domain. The technique compensates for the phase rotation of each frequency component of the signal in the frequency domain, where this procedure enables to form foci at all depths from the data of a single transmit event. We applied the OCT technique with an adaptive beamforming method to IVUS data of a 40 MHz platform in a simulation study.
Results: Figure shows the IVUS image of an artery with and without the proposed method based on the OCT technique, where the fibrous-cap thickness is from 40 to 120 μm. The conventional IVUS depicted blurred interfaces caused by its insufficient axial-resolution. In contrast, IVUS with the proposed method based on the OCT technique depicted interfaces clearly including the fibrous cap. Because the proposed method is applied to IVUS data, the IVUS using the proposed method has the same penetration as the conventional IVUS.



Application of OCT technique to IVUS.

Conclusions: This study reported that the proposed method based on the OCT technique has the high potential to improve the axial-resolution of IVUS to 40 μm using a 40 MHz platform. We believe that IVUS will acquire both penetration and resolution using the OCT technique in the near future.

P6418 | BEDSIDE
Impact of patients' characteristics, procedural, angiographic, and IVUS findings on neoatherosclerosis after stent implantation: Insights from optical coherence tomography study

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Purpose: Recent studies have reported that the development of neoatherosclerosis (NA) inside the stents is associated with late complications such as very late stent thrombosis and late catch up. However, few data exist regarding clinical background of NA after stenting. Therefore, we evaluate the impact of patients' characteristics, procedural, angiographic, and IVUS findings on development of stent-related NA which was detected by optical coherence tomography (OCT).
Methods: We studied 99 stents in 85 patients in which the mean neointimal thickness was >100 μm. The presence of lipid-laden neointima or calcification inside the stents was defined as NA. All lesions were divided into two groups (NA; n=20, and non-NA; n=79), and patients characteristics, procedural, angiographic, and IVUS findings at stent implantation were compared.
Results: As for baseline characteristics, age and total cholesterol level were significantly higher in NA than in non-NA. As for procedural characteristics, duration since stent implantation, especially in BMS, was significantly longer in NA than in non-NA (60.5±44.8 vs. 23.4±24.1 months, $P<0.0001$). Maximum balloon pressure was significantly higher in NA than in non-NA. Interestingly, by IVUS positive remodeling at pre-procedure was frequently observed in NA compared to non-NA. In multivariate analysis, duration since stent implantation and pre-interventional artery remodeling by IVUS remained independent predictors for NA (Table).

Predictors for neoatherosclerosis

	Univariate models			Multivariate model		
	Odds ratio	95% CI	P value	Adjusted Odds ratio	95% CI	P value
Positive remodeling	8.33	2.03–34.3	0.0033	6.64	1.37–32.06	0.0185
Duration since stent implantation	1.03	1.01–1.05	0.0043	1.03	1.00–1.06	0.0235
Total-cholesterol	1.02	1.00–1.03	0.0334	1.02	0.99–1.04	0.1239
DES or BMS	0.27	0.07–1.01	0.0514	0.25	0.04–1.38	0.1105

BMS, bare-metal stent; CI, confidence interval; DES, drug-eluting stent.

Conclusions: These results demonstrate that in addition to the duration since stent implantation, pre-interventional arterial remodeling by IVUS may be related to the development of NA inside the stents.

P6419 | BENCH
Modification of plaque composition and improvement of plaque stability by glucagon-like peptide-1 agonist - In vivo findings using iMap IVUS in Watanabe heritable hyperlipidemic rabbits

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Background: Recent studies reported glucagon-like peptide-1 agonist (GLP-1A) may inhibit aortic atherosclerosis development and formation in Apo-E knockout mice. However, whether GLP-1A stabilizes the fully developed lesion of atherosclerosis or alters the complicated plaque composition is still unclarified.
Methods: Ten Watanabe Heritable Hyperlipidemic rabbits (10- to 12- month-old) were divided into GLP-1A treatment group and control group. After angiography and iMap™ intravascular ultrasound (IVUS) observations, 30 nmol/kg/day Lixisenatide was administrated in GLP-1A group. Same volume of normal saline was administrated in control group. After 12 weeks, after evaluated by angiography and iMap™ IVUS, brachiocephalic arteries were harvested for pathological analysis.
Results: Although IVUS analysis showed no change of plaque burden between 2 groups, GLP-1A treatment indeed changed plaque composition. iMAP IVUS analysis revealed higher %fibrosis (control vs. GLP-1A: 66.3±2.3% vs. 75.1±2.4%, $p<0.01$), lower %necrosis (23.3±2.0% vs. 16.2±2.1%, p=0.02), and lower %calcification (2.2±0.2% vs. 1.0±0.2%, $p<0.01$) in the plaque in GLP-1A group than that in control group. Pathological analysis confirmed iMAP observations. Although the area of vessel, lumen, and plaque is comparable between GLP-1A and control group, GLP-1A treatment improved smooth muscle cell (SMC)-riched plaque (%SMC: 6.93±0.38% vs. 8.14±0.41%, p=0.02) with increased fibrotic contents (%fibrosis: 34.13±1.36% vs. 38.55±1.37%, p=0.02). Furthermore, plaque macrophage infiltration and calcification formation were significantly reduced by GLP-1A (%macrophage: 3.25±0.50% vs. 0.75±0.53%, p=0.02; %calcificaton: 2.31±0.19% vs. 1.35±0.21%, $p<0.01$).
Conclusions: GLP-1A modifies the plaque composition and then improves the stability of fully developed plaque lesions. iMAP is feasible and reliable to identify the plaque characteristics in vivo.

P6420 | BEDSIDE
Assessment of the atherosclerotic plaque at nonculprit lesions with coronary computed tomography angiography in comparison to intravascular ultrasound

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Background: The composition of atherosclerotic plaque has an important influence on the risk of future coronary events. Plaque with attenuation on intravascular ultrasound (IVUS) might be related to deterioration of coronary flow and a worse long-term outcome of coronary artery disease (CAD), while coronary computed tomography angiography (CTA) is the most reliable noninvasive method of evaluating plaque composition. This study aimed to compare detection of attenuated plaques at nonculprit lesions between coronary CTA and IVUS, and to clarify the relations between plaque vulnerability and risk factors for CAD.
Methods and results: We performed coronary CTA in 598 consecutive patients with suspected CAD, among who 82 underwent coronary angiography and percutaneous coronary intervention. In these 82 patients, 210 plaques were evaluated by both coronary CTA and IVUS. Fifty-nine calcified plaques were excluded from analysis. The remaining 151 plaques comprised 50 soft plaques, 51 attenuated plaques, and 50 fibrous plaques. Attenuated plaques had a significantly higher CT density than soft plaques ($P<0.001$) and a significantly lower CT density than fibrous plaques ($P<0.001$). Microcalcification combined with lipid pool-like changes were more frequent in attenuated plaques than in soft plaques ($P<0.05$). Patients with attenuated plaques had significantly lower levels of high-density lipoprotein (HDL) cholesterol than those without attenuated plaques ($P<0.001$).

On multivariate analysis, significant independent predictors of attenuated plaque were low HDL-cholesterol (odds ratio: 0.87, 95% confidence interval: 0.81 to 0.92, P<0.001) and microcalcification combined with lipid pool-like changes (4.53, 1.66 to 12.3, P=0.003).
Conclusions: Analysis of nonculprit lesions by coronary CTA would be useful for detecting the plaque associated with an increased risk of future coronary events.

P6421 | BEDSIDE
Different serial changes of neointimal condition between biodegradable-polymer coated biolimus A9-eluting stents and biocompatible durable-polymer coated everolimus-eluting stents

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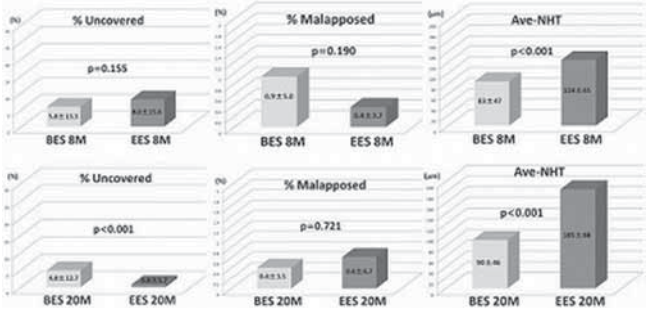
Background: First generation drug-eluting stents (DES) show delayed neointimal coverage of stent struts due to chronic inflammation of durable-polymer, which may cause stent thrombosis. Recently, second generation DESs including biodegradable-polymer coated biolimus A9-eluting stents (BES) whose polymer will be completely absorbed within twelve months, and biocompatible durable-polymer coated everolimus-eluting stents (EES) were available. In this study, we performed serial evaluation of neointimal coverage after BES or EES implantation at eight-month and twenty-month by optical coherence tomography (OCT).
Methods: Serial OCT evaluations were performed in 11 patients with 14 BESs (2243 struts / 250 cross-sections at eight-month, 2061 struts / 260 cross-sections at twenty-month follow-up), and 9 patients with 10 EESs (1269 struts / 154 cross-sections at eight-month, 1229 struts / 158 cross-sections at twenty-month follow-up). We compared uncovered strut proportion (%Uncovered), malapposed strut proportion (%Malapposed), and average neointimal hyperplasia thickness (Ave-NHT) calculated by OCT between BES and EES, at eight-month and twenty-month follow-up, respectively. %Uncovered and %Malapposed were defined as the number of uncovered or malapposed struts divided by observed struts. Ave-NHT was defined as mean value of neointimal hyperplasia thickness on each strut in the same cross-section.
Results: At eight-month, Ave-NHT of EES was significantly higher than BES. At twenty-month, %Uncovered of EES was significantly lower and Ave-NHT of EES was significantly higher than BES (table).



Conclusions: Biocompatible durable-polymer coated EES showed accerelated neointimal healing compared to biodegradable-polymer coated BES, which may have the favorable effects against stent thrombosis.

P6422 | BEDSIDE
Structural remodeling of human coronary vasa vasorum with plaque progression

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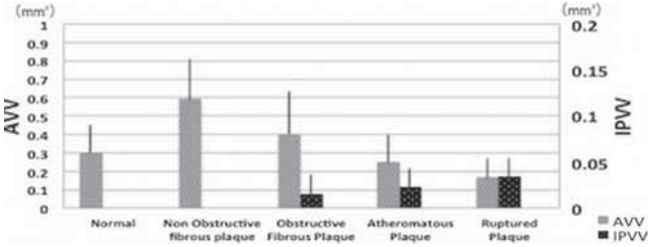
Purpose: Pathological studies have suggested that coronary vasa vasorum (VV) might involve the progression of coronary plaque. However, little is known about relationship between in vivo VV and plaque characteristics. Frequency-domain optical coherence tomography (FD-OCT) has enough penetration depth and spatial resolution to look at both VV surrounding the adventia (AVV) and intra-plaque VV (IPVV). The aim of this study was to investigate the relationship between coronary VV and plaque characteristics using FD-OCT.
Methods: This study consisted of consecutive 43 patients who underwent FD-OCT to explore the left anterior descending artery in 10mm length centered on the first major septal branch irrespective of culprit lesion site. We classified FD-OCT images into five groups: normal (n=10), non-obstructive fibrous plaque (NOFP, n=6), obstructive fibrous plaque (OFP, n=9), atheromatous plaque (AP, n=7), and ruptured plaque (RP, n=11). AVV and IPVV were manually segmented and total volume of VV was quantified by Simpson's method.
Result: Prevalence of IPVV was different among five groups (Normal 0%, NOFP 0%, OFP 44.4%, AP 71.4%, and RP 90.9%, p<0.01). There was significant difference in the volume of AVV and IPVV among the five groups (AVV: Normal 0.303±0.156mm^3, NOFP 0.595±0.225mm^3, OFP 0.401±0.230mm^3, AP 0.250



±0.149mm^3, and RP 0.171±0.099mm^3, p<0.01, IPVV: normal 0.00±0.00mm^3, NOFP 0.00±0.00mm^3, OFP 0.015±0.019mm^3, AP 0.023±0.018mm^3, and RP 0.035±0.019mm^3, p<0.01, respectively, shown in the figure).
Conclusions: AVV is propagated in the beginning of plaque formation. According to change of plaque characteristics, IPVV emerges instead of AVV increase. Our results suggest that structural remodeling of VV closely accompanies with plaque progression.

FUNCTIONAL ASSESSMENT FOR PERCUTANEOUS CORONARY INTERVENTION

P6424 | BEDSIDE
Assessment of microcirculatory resistances after successful angioplasty of obstructed coronary arteries supplying hibernated myocardium can predict functional recovery

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Purpose: To investigate whether assessment of microcirculatory resistances both before and after percutaneous coronary intervention (PCI) may help predicting functional recovery in patients with severe coronary artery disease (CAD) and left ventricular dysfunction due to hibernated myocardium.
Methods: 33 patients with CAD, left ventricular dysfunction and evidence of hibernated myocardium underwent PCI. Functional severity indexes (fractional flow reserve [FFR] and coronary flow reserve [CFR]) and resistance indexes (hyperemic stenosis resistance [HSR] and hyperemic microvascular resistance [HMR]) were measured before and after PCI using a dual sensor pressure-flow wire. Ejection fraction (EF), wall motion score index (WMSI) by transthoracic echocardiography (TTE) and summed rest score (SRS) of myocardial perfusion by 99mTc Tetrofosmin SPECT were measured before PCI and after 3 months.
Results: Overall FFR, HSR and CFR improved significantly after PCI. However, 9 (27%) patients (Group A) showed significantly higher post PCI HMR values as compared to the remaining 24 patients (Group B) (3,01±0,8 vs. 1,35±0,3; p<0,001). From the analysis of the two groups, there were no significant differences in pre PCI FFR, HSR, HMR, CFR, EF, WMSI and SRS. Post PCI FFR, HSR and CFR were not significantly different, as well.
At 3 months, TTE showed a significant improvement of EF (from 34±7% to 42±10%; p<0,01) and WMSI (from 2,08±0,40 to 1,71±0,40; p<0,01) only in group B, as compared to group A (from 39±6% to 42±10% and from 1,92±0,63 to 1,93±0,68; p=NS; p=NS). Similarly, SRS substantially improved only in group B (from 13,1±5,9 to 9,3±6,4; p<0,001), compared to group A (from 10,6±8,9 to 9,2±9,2; p=NS).
Conclusions: Persistently high HMR values measured after successful PCI can predict lack of improvement of left ventricular function and myocardial perfusion in patients with obstructive CAD and evidence of hibernated myocardium.

P6425 | BEDSIDE
Efficacy of contrast medium induced Pd/Pa ratio in predicting functional significance of intermediate coronary artery stenosis assessed by fractional flow reserve: the RINASCI study

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Purpose: A critical prerequisite for the assessment of the functional significance of coronary stenosis by Fractional Flow Reserve (FFR) is the achievement of maximal hyperemia using adenosine. Nevertheless, both the intra-venous (i.v.) and the intra-coronary (i.c.) routes have several drawbacks that limit the widespread application of FFR in the real world. Radiographic contrast medium induces sub-maximal reactive hyperemia. We hypothesized that Pd/Pa ratio registered during sub-maximal reactive hyperemia induced by i.c. injection of conventional non-ionic radiographic contrast medium (Contrast Medium induced Pd/Pa Ratio: CMR) can be sufficient for the assessment of physiological severity of stenosis in the vast majority of cases. The aim of the present study was to test the accuracy of CMR in comparison to FFR.
Methods: 104 intermediate coronary stenoses were prospectively and consecutively enrolled. CMR was obtained after i.c. injection of 6 ml of radiographic contrast medium, while FFR was measured after i.c. (600 μg) or i.v. (140 μg/kg/min) administration of adenosine.

Results: Despite CMR values were significantly higher than FFR values (0.88 [IR 0.80-0.92] vs 0.87 [IR 0.83-0.94], p<0.001), a strong correlation between CMR and FFR values was observed (r=0.94, p<0.001) with an excellent agreement at Bland Altman analysis (95% CI of disagreement: -0.029 to 0.072). ROC curve analysis showed an excellent accuracy of CMR cut-off of ≤0.83 in predicting FFR value ≤0.80 (AUC 0.97 [CI 95%, 0.91-0.99, specificity 96.1, sensitivity 85.7]. Moreover no FFR value ≤0.80 corresponded to a CMR≥0.88.
Conclusions: CMR, a novel index obtained during sub-maximal hyperemia induced by conventional radiographic contrast medium, is accurate in predicting the functional significance of a coronary stenosis evaluated by FFR. This could allow limiting use of adenosine to obtain FFR to doubtful cases. In particular, we suggest to consider significant a CMR value≤0.83, not significant a CMR value≥0.88 and to induce maximal hyperemia using adenosine for FFR assessment when CMR is between 0.84 and 0.87.

P6426 | BEDSIDE
Pressure-derived coronary flow reserve cannot be used as an alternative for coronary flow velocity reserve

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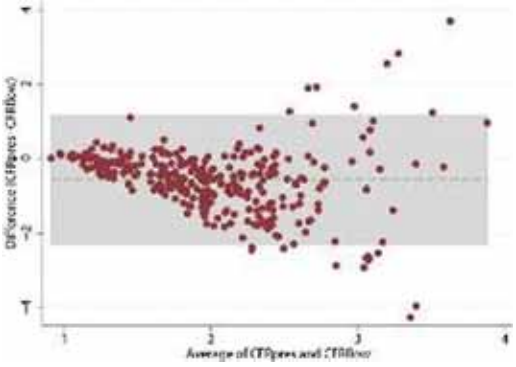
Purpose: Calculation of CFR from coronary pressure measurements (CFRpres) has been proposed as an alternative to Doppler flow velocity derived CFR (CFRflow). CFRpres is defined as the ratio between the square root of the pressure-drop across the stenosis during hyperaemia and at baseline. This simplified model neglects the effects of stenosis geometry on flow impediment, raising concerns on its validity. We sought to validate CFRpres against CFRflow in a large cohort of coronary stenoses of intermediate severity.
Methods and results: A total of 299 coronary stenoses from 228 patients were evaluated by means of intracoronary pressure and flow velocity measurements. CFRflow was calculated as the ratio of hyperaemic average peak flow velocity (APV) to APV during basal conditions and CFRpres as indicated above. CFRflow was higher than CFRpres [median 2.21 (Q1, Q3: 1.70, 2.76 vs 1.55 (Q1, Q3: 1.29, 1.91; p<0.001]. There was a moderate overall linear correlation between CFRflow and CFRpres (r=0.426 p<0.001; R2=0.18). Bland Altman analyses showed a mean bias of -0.56±0.89, with a proportional error of -0.30 (p=0.001) and significant heteroscedasticity (95% limit of agreement: -0.56±1.74). Moreover, categorical agreement at the 2.0 clinical cut point of CFRflow was low (κ=0.171, p<0.001). When stratified at the clinical 2.0 CFRflow cut-off value, the 95% limits of agreement amounted to -0.98±1.61 and 0.04±1.31 for CFRflow ≥2.0 and CFRflow <2.0, respectively.



Bland Altman plot CFRpres versus CFRflow.

Conclusions: CFRpres systematically underestimates CFRflow values, and its magnitude of deviation is related to the magnitude of underlying CFRflow. Hence, CFRpres cannot be used as an alternative to CFRflow.

P6427 | BEDSIDE
Caffeine attenuates intravenous adenosine-induced hyperemia in Fractional Flow Reserve measurement

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Purpose: The interaction between caffeine and adenosine is still a matter of debate. Conflicting results have been reported in the literature concerning the effect of caffeine on adenosine stress single-photon emission computed tomography using intravenous adenosine. In the measurement of fractional flow reserve (FFR), there is limited data using intracoronary adenosine in a small number of subjects. The aims of this study were to examine if caffeine attenuates intravenous adenosine-induced hyperemia and if increased doses of adenosine overcomes the caffeine antagonism in the FFR measurement.
Methods: FFR was measured using different adenosine doses (140, 175, and 210 μg/kg/min) and papaverine as a reference standard in patients with intermediate coronary stenoses, who refrained from caffeine for >24 h (no caffeine group; n=16) and those who consumed caffeine (caffeine group; n=31). Serum caffeine concentrations were measured just before the administration of adenosine.
Results: Due to side effects, adenosine was discontinued at a dose of 175 μg/kg/min in one patient in the caffeine group and at a dose of 210 μg/kg/min in two in each of the groups. The median caffeine levels in the caffeine group was 2.9 mg/l (interquartile range: 1.8-4.6 mg/l). In the caffeine group, adenosine overestimated FFR (140 μg/kg/min: 0.813, p<0.001; 175 μg/kg/min: 0.806, p<0.01; 210 μg/kg/min: 0.794, p=0.01) compared with papaverine (0.779). In the no caffeine group, FFR with adenosine did not decrease above the dose of 140 μg/kg/min (0.769, 0.771, and 0.770 at 140, 175, and 210 μg/kg/min, respectively) and was not significantly different from that with papaverine (0.765). The difference in FFR between papaverine and 140 μg/kg/min dose of adenosine was significantly greater in the caffeine group than in the no caffeine group (0.034 vs. 0.004, p<0.05). Using the cutoff value of ≤0.80, false-negative results were demonstrated in 5/16, 4/16, and 2/16 patients in the caffeine group at doses of 140, 175, and 210 μg/kg/min, respectively; whereas, none had a false-negative result in the no caffeine group.
Conclusions: Caffeine attenuates intravenous adenosine-induced hyperemia in the FFR measurement. An increase in adenosine dose up to 210 μg/kg/min cannot fully surmount the antagonism, and concerns about tolerability and safety remained. Our results suggest that abstention from caffeine is necessary before adenosine stress testing to avoid submaximal hyperemia.

P6428 | BEDSIDE
Can intracoronary nitroglycerin Pd/Pa predict fractional flow reserve with intravenous or intracoronary adenosin?

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Introduction: Functional assessment of coronary artery stenosis is performed by measuring the fractional flow reserve (FFR) under hyperemic conditions (Adenosine). But the use of Adenosine have several limitations such as; high cost and adverse systemic effects. Recent studies have tried to find a correlation between different parameters (iFR, Baseline Pd/Pa) obtained without adenosine and FFR. Objective: We sougth to investigate the relationship and correlation between FFR and the Pd/Pa value obtained after the intracoronary infusion of nitroglycerin (Pd/Pa-NTG) and if this parameter enhances diagnostic accuracy for FFR prediction compared to the resting baseline Pd/Pa measurement.
Methods: From February 2013 through September 2013 we conducted a multicenter study that prospectively included 335 consecutive pressure wire data sets from 281 patients presenting intermediate coronary artery lesions (30-70% by QCA estimation). Patient demographic and angiographic lesion data were collected. Resting baseline Pd/Pa, Pd/Pa-NTG after coronary infusion of a 2 mcg bolus of nitroglycerin and FFR after continuous intravenous (iv) adenosine infusion (140 μg/kg/min) or after intracoronary (ic) adenosine infusion (≥360 mcg in the left system and ≥90 mcg in the right coronary artery), were measured following a standard protocol in all the centers.
Results: Resting baseline Pd/Pa value was 0.72 to 1.0 (0.93±0.04), Pd/Pa-NTG was 0.60 to 1.0 (0.87±0.07) and FFR value after Adenosine iv or ic 0.55 to 1.0 (0.83±0.08). The ROC curves for resting baseline Pd/Pa and for Pd/Pa-NTG, using a FFR ≤0.80 as the reference standard variable showed an AUC of 0.88 (95% CI=0.84-0.92, p<0.001) and 0.94 (95% CI=0.92-9.96, p<0.001) respectively. The optimal cutoff values of resting baseline Pd/Pa and Pd/Pa-NTG for the prediction of FFR >0.80, were >0.96 and >0.88 respectively. These values were present in a 29.8% (n=100) and a 47.1% (n=158), of the total data sets. Scatter plots of resting baseline Pd/Pa and Pd/Pa-NTG, showed a better corelation and agreement points, with Pd/Pa-NTG than baseline Pd/Pa. Sensitivity and NPV of the Pd/Pa-NTG>0.88 were consistently high in all the subgroup analysis.
Conclusion: The Pd/Pa-NTG shows a good correlation with FFR in the intermediate lesions, even better than that with resting baseline Pd/Pa. The cutoff value of Pd/Pd-NTG >0.88 has an excellent NPV and sensitivity for determining lesion significance allowing to avoid adenosine-FFR determination in almost half of patients. This excellent diagnostic performance is not affected by angiographic or methodological variables (adenosine iv or ic).

P6429 | BEDSIDE
An overlooked parameter in coronary slow flow phenomenon: whole blood viscosity

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Purpose: Coronary slow flow phenomenon (CSFP) is a clinical entity with poorly understood pathogenesis. Blood viscosity by using various methods has been

studied in CSFP previously. However, there was scarce data about the association of CSFP with whole blood viscosity (WBV) which was known as a neglected parameter of Virchow triad. Therefore, in this study we aimed to assess the relationship between CSFP and WBV.
Methods: A total of 226 patients (64,8% male, mean age 51,4±9,7) with CSFP and 207 subjects (62,5% male, mean age 52,9±11,2) with normal coronary arteries as control group were enrolled. CSFP was quantified by means of corrected thrombolysis in myocardial infarction (TIMI) frame count and WBV was calculated from hematocrit and plasma protein concentration at low shear rate (LSR) (0.5 sec-1) and high shear rate (HSR) (208 sec-1) by a validated equation.
Results: CSFP patients had significantly higher WBV for both LSR (75.5±15.0 vs 63.9±21.5, $p<0.001$) and HSR (18.0±0.95 vs 17.2±0.95, $p<0.001$). Correlation analysis revealed a significant relationship between the corrected TIMI frame count and WBV for LSR ($r=0.710$; $p<0.001$) and HSR ($r=0.641$; $p<0.001$). A cut-off value of 69.3 WBV for LSR has a 76% sensitivity and 70% specificity for prediction of CSFP (AUC: 0.819). A cut-off value of 17.4 WBV for HSR has a 75.2% sensitivity and 71.5% specificity for prediction of CSFP (AUC: 0.845).

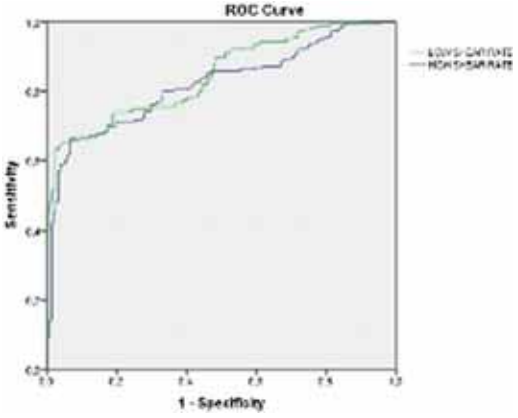

Figure 1

Conclusion: WBV is a simple, available and non-invasive test with low cost for evaluation of blood viscosity. Our study results demonstrated a significant and independent association between CSFP and WBV. The extrapolation of WBV with this method may utilize evaluating cardiovascular diseases where stasis has an important pathophysiological role.

P6430 | BEDSIDE
Two different thermodilution-derived coronary blood flow patterns immediately after coronary intervention with TIMI 2 flow in patients with ST-segment elevation myocardial infarction

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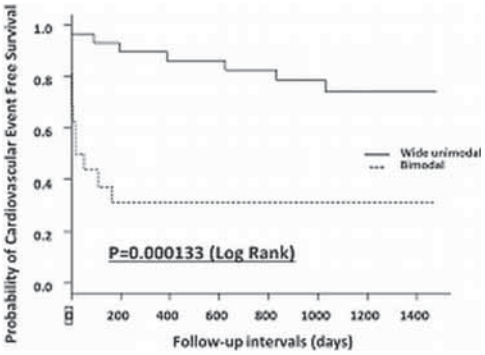
Background: A recent study reported the thermodilution-derived coronary blood flow pattern (CBFP) after percutaneous coronary intervention (PCI) associated with cardiac events in ST-segment elevation myocardial infarction (STEMI) patients. Although TIMI 2 flow leads to patient's outcome worse, all patients with TIMI 2 flow after PCI do not have always poor outcomes. This study evaluates whether the CBFP predicts the clinical risk stratification in patients with TIMI 2 flow after PCI.
Methods: Forty-five patients with TIMI 2 flow after PCI were enrolled prospectively in this study. Using a pressure sensor/thermistor-tipped guidewire, CBFP was assessed from the thermodilution-curves after PCI. CBFP was classified into 2 groups according to the shape of thermodilution-curve: a wide-unimodal (n=29), or bimodal (n=16). Peak CPK, Wall-motion score index (WMSI) and microvascular obstruction (MVO) appearance assessed by cardiovascular magnetic resonance were analyzed within 2 weeks after PCI. Cardiac events were defined as cardiac death and/or heart failure re-hospitalization within this study period.



Results: Median follow-up period was 2.4 years. Although there were no significant differences in peak CPK, WMSI and MVO appearance between 2 groups, patients in bimodal had a higher risk of cardiac events during this study period ($p=0.00013$). Multivariate analysis revealed that bimodal was the only independent predictor of cardiac events in patients with TIMI 2 flow (hazard ratio, 4.95; 95% confidence interval, 1.71-14.34; $P=0.0032$).
Conclusions: A bimodal-shape is associated with the poor outcomes in patients with TIMI 2 flow. This easily assessable CBFP is useful in long-term clinical risk stratification for STEMI patients with TIMI 2 flow at the catheterization laboratory immediately after PCI.

P6431 | BEDSIDE
Diagnostic impact of resting distal coronary pressure to aortic pressure to predict physiological lesion severity

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Background: Although fractional flow reserve (FFR) was useful modality to identify physiological lesion severity, it was necessary to obtain pharmacological hyperemia. However, we sometimes encounter adverse events such as atrioventricular block and hypotension. It was unclear whether the resting distal coronary pressure to aortic pressure (Pd/Pa) index could predict physiological significant stenosis without hyperemic stimulus. Thus, we evaluated the relationship between resting Pd/Pa and FFR in various coronary lesions.
Method: A total of 200 consecutive patients with 285 intermediate lesions were confirmed in this study. After pressure wire was positioned as distal as possible in a coronary artery, we measured the resting Pd/Pa index before pharmacological stress. Then, we measured FFR with intravenous adenosine triphosphate. Physiological significance was defined as FFR less than or equal 0.80.
Results: Analyzed vessels were distributed in left anterior descending (LAD, 52%), left circumflex (26%), and right coronary artery (22%), respectively. In all lesions, reference diameter, diameter stenosis were 2.7±0.6 mm, 59±13%, respectively. The resting Pd/Pa index showed a strong correlation with FFR ($r=0.84$, $p<0.0001$). These strong correlations showed no difference in LAD and non-LAD ($r=0.82$ and $r=0.84$, respectively). In overall lesions, the best cut-off value of the resting Pd/Pa index to predict physiological significance was 0.92, which had 90% sensitivity and 82% specificity (area under the curve: AUC 0.93, positive predictive value: PPV 90%, negative predictive value: NPV 85%, and accuracy 87%) from receiver operating characteristic (ROC) curve. In LAD lesions, the best cut-off value was 0.89, which had 77% sensitivity and 97% specificity (AUC 0.93, PPV 99%, NPV 57%, and accuracy 77%). In non-LAD lesions, the best cut-off value was 0.91, which had 83% sensitivity and 91% specificity (AUC 0.93, PPV 87%, NPV 88%, and accuracy 88%). The resting Pd/Pa more than 0.97 (n=47, 16%) had 100% of NPV, and less than 0.84 (n=75, 26%) had 100% of PPV in all lesions.
Conclusion: The resting Pd/Pa index had a good linear relationship with FFR. Although it was not based on physiological concept, a certain range of the resting Pd/Pa might predict functional significance without inducing pharmacological hyperemia for lesion assessment.

P6432 | BEDSIDE
Impact of patients hemodynamic status on the accuracy of fractional flow feserve measurement

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Purpose: Fractional flow reserve (FFR) is invasive index to assess the ischemic potential of coronary stenoses. FFR is calculated as the ratio of average distal coronary (Pd) to aortic pressure (Pa) during maximal hyperemia. Mean central venous pressure (Pv) is neglected in the formula as considered of little impact

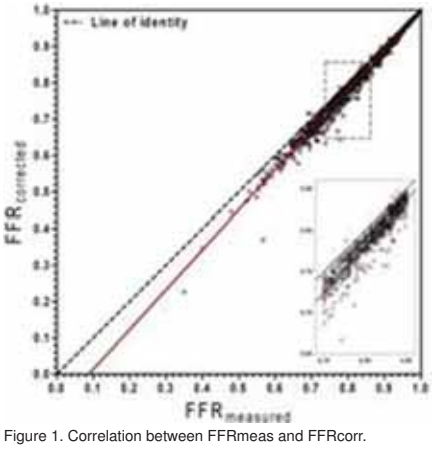

Figure 1. Correlation between FFRmeas and FFRcorr.

if within normal range. We aimed at investigating the impact of Pv over a wide range on FFR measurement.
Methods: We obtained measured FFR (FFRmeas=Pd/Pa) and corrected FFR (FFRcorr= Pd-Pv/Pa-Pv) in 1593 intermediate coronary stenosis of 1181 patients (pts) undergoing left and right heart catheterization because of ischemic heart disease (639 [54%]), heart failure (597 [51%]) or valve disease (583 [49%]). Average blood pressure was 91±17 mmHg and median Pv was 7 mmHg (max 27 mmHg).
Results: The correlation between FFRcorr and FFRmeas was excellent (R2=0.985, p<0.001; slope 1.095±0.003; see Figure). Median FFRmeas (0.85 [0.78; 0.91]) was slightly but significantly higher than median FFRcorr (0.83 [0.76; 0.90], p<0.0001). The median difference between FFRcorr and FFRmeas was 0.01 (0.01; 0.02). Values of FFRmeas above the cut-off of 0.80 turned to an FFRcorr below 0.80 in 92 (6%) stenoses overall, and in 29 (9%) (p=0.021 vs. overall) stenoses of pts with Pv higher than 10 mmHg. Stenoses with FFRmeas over 0.83 never turned to an FFRcorr below 0.80. No FFRmeas value decreased from >0.80 to a FFRcorr<0.75.
Conclusions: FFR values above the gray zone (i.e. >0.80) did not turn to values below the gray zone (i.e. <0.75) in any case, suggesting that the impact of the hemodynamic status on FFR measurement is indeed negligible, even in patients with markedly increased Pv.

P6433 | BEDSIDE
Intermediate term reproducibility of microvascular resistance measurements by the index of microcirculatory resistance in patients with intermediate coronary artery stenosis

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Background: Compared with coronary flow reserve (CFR), the index of microcirculatory resistance (IMR) has been shown to provide a more reproducible assessment of the microcirculation, which is independent of epicardial coronary artery stenosis severity and hemodynamic status. However, intermediate-term reproducibility of IMR has not been investigated.
Methods and results: Using a pressure-temperature sensor-tipped coronary wire, IMR and thermodilution-derived CFR (ThermoCFR) were measured twice, along with FFR, in 36 coronary arteries with intermediate lesion with an average interval of 44±22 days (range 8–121). Hemodynamic status of aortic pressure, distal coronary artery pressure, and heart rate were similar between the 2 measurements. There were no significant differences in IMR, ThermoCFR, and FFR between the 2 measurements (IMR: 21.7±10.6 vs 19.9±9.4, ThermoCFR: 3.18±1.67 vs 3.54±1.77, FFR: 0.76±0.06 vs 0.77±0.08, respectively). Regression analysis showed a significant relationship between the 2 measurements for all three values (IMR:R2=0.31, p<0.001, ThermoCFR:R2=0.25, p=0.002, and FFR:R2=0.65, p<0.001, respectively). The repeatability coefficients and relative repeatability coefficients of IMR, ThermoCFR, and FFR were 18.5 (88.9%), 3.40 (101.2%), and 0.08 (10.4%), respectively. Coefficients of variation of IMR, ThermoCFR, and FFR were 32.3%, 36.7%, and 3.9%, respectively.
Conclusion: The intermediate term longitudinal reproducibility of IMR was similar to ThermoCFR and significantly lower than that of FFR. This variability should be taken into consideration when IMR is used for the interpretation of microvascular resistance.

P6434 | BEDSIDE
Relationship between index of microcirculatory resistance and fraction flow reserve in patients with coronary artery disease

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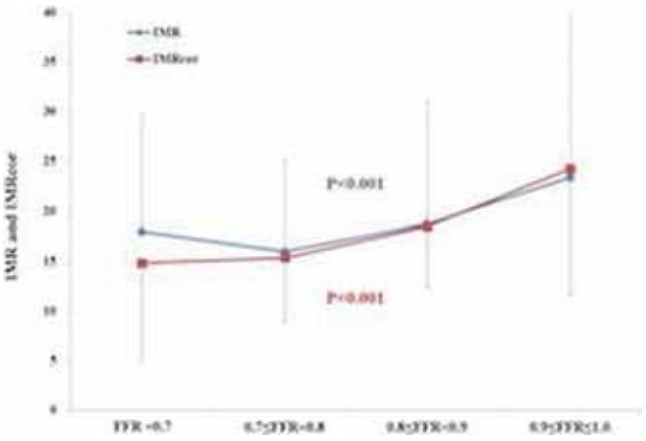
Purpose: The relationship between microcirculatory dysfunction and severity of epicardial coronary artery disease in patients with coronary disease is not well-known. We performed this study to investigate the relationship between index of microcirculatory resistance (IMR) and fractional flow reserve (FFR) in patients who underwent elective coronary angiography and invasive physiologic assessment.
Methods: 852 vessels with available IMR and FFR were consecutively enrolled. Patients with unstable clinical condition, ST-elevation myocardial infarction, and flows lower than TIMI3 were excluded. IMR and FFR were measured using a pressure-temperature sensor-tipped guidewire at the same location of a target vessel. Hyperemia was induced by adenosine infusion of 140ug/kg/min. Corrected IMR (IMRcor) which accounts for collateral flow was derived by Yong's formula.
Results: Mean FFR, IMR and IMRcor were 0.87±0.09, 20.6±16.2 and 20.7±17.3 (interquartile range: 12-23), respectively. The difference between IMR and IMRcor was the highest in patients with lowest FFR. There was a positive correlation between FFR and IMRcor (r=0.216, p=0.007) (Figure). Using the cut-off value of FFR 0.8 and IMRcor 23, 17.8% of low FFR and 28.5% of high FFR had microvascular dysfunction.



The relationship between IMR and FFR.

Conclusion: Integration of macro- and microvascular function using FFR and IMR is needed to comprehensively assess the pattern of atherosclerotic disease in patients with ischemic heart disease.

P6435 | BEDSIDE
Thermodilution-derived coronary blood flow pattern immediately after coronary intervention as a predictor of long-term clinical outcomes in patients with ST-segment elevation myocardial infarction

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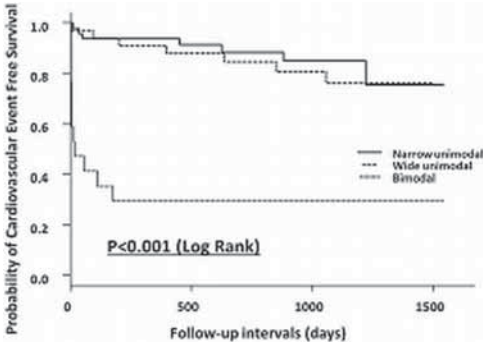
Background: A recent study reported that coronary blood flow (CBF) can be evaluated by analyzing thermodilution-curve that is measured with a pressure sensor/thermistor-tipped guidewire during percutaneous coronary intervention (PCI). Bimodal-shape of thermodilution-curve was associated with microvascular damage after ST-segment elevation myocardial infarction (STEMI). However it is unknown whether the bimodal-shape predicts mortality and re-hospitalization for heart failure in long term period for patients experiencing STEMI.
Methods: Between September 2009 and August 2012, 97 consecutive patients with a first STEMI were prospectively enrolled in this study. CBF pattern was assessed from the thermodilution-curves after successful PCI at maximum hyperemia. CBF pattern was classified into 3 groups according to the shape of thermodilution-curve: a narrow-unimodal (n=47), a wide-unimodal (n=33), or bimodal (n=17). Major adverse cardiac events (MACE) were defined as cardiac death and/or heart failure re-hospitalization within this study period.
Results: Median follow-up period was 2.4 years. Although patients in the narrow-unimodal group and the wide-unimodal group had a significantly lower incidence of MACE, patients in bimodal group had a higher risk of MACE during this study period (71, 15, 21%, p<0.001). Multivariate analysis revealed that bimodal shape of the thermodilution-curve was the only independent predictor of MACE after STEMI (hazard-ratio, 8.38; 95% confidence-interval, 2.13–33.00; P=0.0023).



CBF pattern in long-term outcomes.

Conclusions: A bimodal-shape of the thermodilution-curve is associated with the poor long-term clinical outcomes. This easily assessable coronary flow pattern is useful in clinical risk stratification for STEMI patients in the cardiac catheterization laboratory immediately after PCI.

EXPERIMENTAL STUDIES IN CORONARY ARTERY DISEASES

P6437 | BEDSIDE
Statin treatment increases the circulating endothelial progenitor cells and improve endothelial function in patients with coronary artery diseases

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Background: Statin use in patients with coronary artery disease (CAD) is associated with reduction in cardiovascular events occurring independently of statin lipid-lowering effects. Statins improve endothelial function and endothelial progenitor cells (EPC) differentiation in patients with CAD.
Purpose: To study the impact of statin therapy on number and function of EPCs in patients with CAD. Also, the assessment of the effect of statin on endothelial function estimated by brachial artery flow mediated dilation (FMD).
Methods: We assessed EPCs percentage and functions in 81 patients: 41 patients with acute coronary syndrome (ACS) (group 3) and 40 with chronic stable angina (group 2), in addition to 24 control subjects (group 1). Groups 2 &3 were divided into subgroups (A: not on statin & B: on statin). EPCs were identified on the basis of KDR cell surface marker expression (VEGFR-2). EPCs function was assessed by quantitative vWF and VEGFR-2 genes expression and eNOS protein level measurement. Brachial artery FMD was estimated to assess the effect of statin on endothelial function.
Results: KDR antigen was highly significant expressed on EPCs surface in patients on statins therapy (group 2B, 3B) compared to patients not on statins therapy (group 2A, 3A) ($P<0.001$). Flow Cytometry percentage shows high significant difference between patients on statins therapy (2B, 3B) and patients not on statins therapy (2A, 3A) ($P<0.001$). The highest significant difference was found in patients on statins treatment (2B, 3B) compared to control and patients not on statins treatment (2A, 3A). Parameters of EPCs function revealed a significant increase in quantitative levels of VEGFR-2 and vWF genes expression and eNOS protein level were detected in patients on statins treatment versus patients not on statins treatment (group 2B, 3B) versus (group 2A, 3A) ($P<0.001$). FMD was significantly higher in patients on statin (group 2B, 3B) versus patients not on statins therapy (group 2A, 3A) ($P<0.001$) There was a positive correlation ($r=0.723$) between FMD percentage and plasma eNOS biomarker in patients on statins treatment (group 2B, 3B). There was also a high positive ($r=0.475$) correlation between KDR flow cytometry percentages and FMD.
Conclusions: Statin therapy increases the circulating EPCs and improve endothelial function in patients with CAD. EPCs number was the strongest predictor of FMD. FMD is an indicative test for eNOS bioavailability production.

P6438 | BEDSIDE
New insights into the mechanism of hyperglycemia in non-diabetic patients with acute coronary syndromes

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Purpose: Stress generated by acute illness is associated with insulin resistance and hyperglycemia. In patients with acute coronary syndrome (ACS), stress hyperglycemia (SH) has been linked to worse prognosis but its physiopathological substrate has not been elucidated. In this study we aim to asses if SH is associated with higher levels of cortisol, GH, catecholamines and insulin resistance.
Methods: Prospective cohort study. We included patients admitted with diagnosis of ACS between December 2011 and September 2013. On admission, glucose, insulin, cortisol, GH, adrenaline y noradrenalin were dosed and HOMA-IR was calculated. Patients were divided into 3 groups: G1=normal subjects (non-diabetics with glucose $<$126mg/dl), G2=SH (non-diabetics with glucose $\geq$126mg/dl), G3= diabetics. For statistical analysis, χ^2 test was used for discrete variables and ANOVA or Student T test for continuous variables. A p value <0.05 was considered significant in all cases.
Results: Ninety three patients were included, mean age 70.7 ($\pm$12,6) years, 49.5% male. Forty seven patients (50.5%) were included in G1, 18 (19,4%) in G2 and 28 (30,1%) in G3. There was no significant difference in age, sex and prevalence of cardiovascular risk factors between groups. Table 1 summarizes the main results. Cortisol was significantly higher in G2 compared to G1 (22.3$\pm$10.5 vs 12.6$\pm$9.1 respectively; p=0,002) and in the limit of significance compared to G3 (22,3$\pm$10,5 vs 14,9$\pm$10,7; p=0,057). No statistically significant difference in insulin, GH, HOMA-IR, adrenalin and noradrenalin was noted between groups.

Table 1. Main results

	G1	G2	G3	P
Cortisol (μg/dl)	12.6$\pm$9.1	22.3$\pm$10.5	14.9$\pm$10.7	0.01
GH (ng/ml)	0.9$\pm$1.2	1.4$\pm$3.9	1.67$\pm$2.6	0.59
Insulin (μU/ml)	19.8$\pm$35	11$\pm$5.8	13.7$\pm$9.3	0.63
HOMA-IR	5.1$\pm$9	4.2$\pm$2.3	7.49$\pm$6	0.5
Adrenaline (pg/ml)	63.8$\pm$48	57.3$\pm$75	78.7$\pm$66	0.58
Noradrenaline (pg/ml)	96$\pm$57	90$\pm$75	109$\pm$77	0.77

Conclusion: Stress hyperglycemia could be caused by exaggerated cortisol adrenal response and its consequent glycogenolysis and not by higher resistance to insulin or catecholamine secretion.

P6439 | BEDSIDE
CSL112 robustly enhances the ability of serum to efflux cholesterol in normal healthy adults and patients with atherothrombotic disease

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Purpose: ApoA-I is known to remove cholesterol from atherosclerotic plaque. CSL112 is a novel formulation of apoA-I purified from human plasma and reconstituted to form HDL particles suitable for infusion which is currently in development for acute coronary syndrome (ACS). Phase 1 (NCT01129661, NCT01281774) and Phase 2a (NCT01499420) have demonstrated favourable safety, pharmacokinetic (PK) and biomarker responses to infusions of CSL112 in normal healthy subjects (NHS) or patients with stable atherothrombotic disease (ATD). Here we quantitatively compare the biomarker responses in the NHS populations versus the ATD population.
Methods: We compared key biomarker data from the three studies; formation of very small HDL, elevation of total cholesterol efflux capacity from macrophages and movement of cholesterol to HDL. We calculated the baseline corrected area under the curve (AUC) of each biomarker for each subject and the corresponding baseline corrected AUC for apoA-I.
Results: Linear regression analysis of individual biomarker AUC over apoA-I AUC across the 3 different studies showed similar responses in patients with ATD compared to NHS. Figure 1 shows the relationship to total cholesterol efflux.

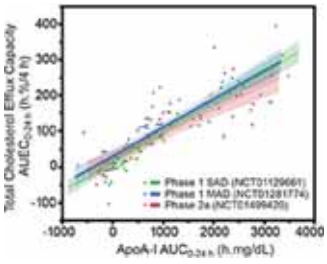

Figure 1

Conclusions: CSL112 in patients with ATD immediately enhances biomarkers of reverse cholesterol transport to a similar extent as in NHS. CSL112 may thus provide a novel option to rapidly lower the systemic burden of atherosclerosis and to reduce the risk of recurrent events following ACS.

P6440 | SPOTLIGHT
The safety and efficacy of intracoronary nitrite infusion during acute myocardial infarction (NITRITE-AMI): a single centre, randomised, double-blind controlled trial

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Introduction: Pre-clinical evidence demonstrates that inorganic nitrite, following its in situ conversion to nitric oxide, attenuates consequent myocardial reperfusion injury. In this study we sought to determine whether a significant improvement in infarct size can be achieved by the intra-coronary injection of nitrite during primary percutaneous coronary intervention (PCI) in acute myocardial infarction.
Methods: In this double-blind, placebo-controlled trial, we randomly assigned 80 patients presenting with acute ST-elevation myocardial infarction to receive either an intracoronary bolus (10 ml) of sodium nitrite (1.8 μmol in normal saline: nitrite group) or normal saline (placebo group) distal to the occlusion site before initial balloon inflation during primary PCI. The primary endpoint was infarct size assessed by measuring the release of creatine kinase, secondary outcomes included infarct size assessed by troponin T release, infarct size and myocardial salvage index (MSI) assessed by cardiac magnetic resonance imaging (CMR) and major adverse cardiac events (MACE) at 1 year.
Results: The nitrite and control groups were similar with respect to baseline characteristics except for a longer ischaemia time in the nitrite group (p=0.031). There were no differences in release of serum creatine kinase (p=0.92) or troponin T (p=0.85) after reperfusion between the nitrite and control groups. No difference was seen in CMR assessed infarct size (p=0.254) but there was a trend to improved MSI in the nitrite group (mean 0.52 [95% confidence intervals [CI] of 0.46 to 0.58] vs. 0.44 [95% CI of 0.39 to 0.50], p=0.051). However, there was a difference in 1 year MACE (2.6% in the nitrite group vs 15.8% in the control, p=0.04). In a subgroup of 66 patients with TIMI $\leq$1 flow at time of intervention there was a decrease in the release of serum creatine kinase in the nitrite group (p=0.030),

with no difference in troponin T release (p=0.158). CMR analysis indicated a 19% reduction in infarct size (p=0.034), 35% reduction in microvascular obstruction and increased MSI (p=0.002) in the nitrite treated sub-group patients. No adverse effects of nitrite administration were detected.
Discussion: In this study population intra-coronary nitrite infusion is safe but, despite reducing MACE at 1 year, has no significant effect on infarct size. In contrast, in a sub-group of patients with TIMI flow≤1, infarct size was reduced indicating that intra-coronary nitrite administration to the culprit vessel of selected patients presenting with AMI may provide a new therapeutic adjunct to PCI. Further investigation is warranted.

P6441 | SPOTLIGHT
Angiotensin receptor blocker therapy in patients with ST-segment elevation myocardial infarction with preserved left ventricular systolic function

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Objective: To investigate the association of ARB therapy with clinical outcomes in ST segment elevation myocardial infarction (STEMI) patients with preserved left ventricular (LV) systolic function.
Background: Limited data are available on the efficacy of angiotensin receptor blocker (ARB) therapy for secondary prevention in STEMI patients with preserved LV systolic function.
Methods: Between November 2005 and September 2010, 20344 patients with acute MI were enrolled in a nationwide, multi-center registry. Among these, we studied STEMI patients who underwent primary percutaneous coronary intervention and LV ejection fraction ≥40%. We classified patients into the ARB group (n=1185), the angiotensin converting enzyme (ACE) inhibitor group (n=4564), and the no renin-angiotensin system (RAS) blocker group (n=949) according to the use of ARB or ACE inhibitors at discharge. Propensity-score matching analysis was also performed. The primary outcome was cardiac death or MI.
Results: The median follow-up duration was 371 (interquartile range: 167 to 450) days. Cardiac death or MI occurred in 21 patients (1.8%) of the ARB group, 77 patients (1.7%) of the ACE inhibitor group, and 33 patients (3.5%) of the no RAS blocker group. The ARB group had a similar risk of cardiac death or MI compared with the ACE inhibitor group (hazard ratio [HR], 1.02; 95% confidence interval [CI], 0.63-1.66; P=0.92) and a lower risk of cardiac death or MI compared with the no RAS blocker group (HR, 0.44; 95% CI, 0.25-0.76; P=0.004). After propensity-score matching (1175 pairs), there was no significant difference in the rate of cardiac death or MI between the ARB group and the ACE inhibitor group (adjusted HR, 0.65; 95% CI, 0.30-1.38, P=0.65). The ARB group still had a lower rate of cardiac death or MI than the no RAS blocker group in matched population (803 pairs) (adjusted HR, 0.35; 95% CI, 0.14-0.90; P=0.03).
Conclusions: ARB showed beneficial effects comparable to ACE inhibitors in STEMI patients with preserved LV systolic function. Our results suggest that ARBs can be alternatives to ACE inhibitors in STEMI patients with preserved LV systolic function.

P6442 | BEDSIDE
Effect of direct renin inhibitor on left ventricular remodeling in patients with primary acute myocardial infarction

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Purpose: Some patients with acute myocardial infarction (AMI) have a poor prognosis due to left ventricular remodeling (LVR), resulting in the recurrence of congestive heart failure even when therapy with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II type 1 receptor blockers (ARBs) has been initiated. We investigated the effect of early administration of the direct renin inhibitor (DRI) aliskiren in combination with an ACEI or an ARB on LVR using cardiac magnetic resonance (CMR) imaging in patients with primary AMI.
Methods: The study population included 60 consecutive AMI patients. Overall, 18 patients were excluded from the study according to the following criteria: a history of MI (n=3), renal insufficiency with baseline serum creatinine >1.5 mg/dL (n=2), atrial fibrillation (n=2), cardiogenic shock or unstable hemodynamic status (n=8), and AMI for >12 hours from onset of symptoms (n=3). The remaining 42 primary AMI patients who underwent percutaneous coronary intervention successfully within 12 hours from the onset of AMI were enrolled. Twenty-one consecutive patients were treated with an ACEI or an ARB (non-DRI group), and another 21 consecutive patients received aliskiren combined with an ACEI or an ARB (DRI group). CMR imaging was performed 7 days after AMI and 10 months later.
Results: CMR imaging revealed no significant changes in LV end-diastolic volume (-15.3±22.3 vs. -20.8±23.0 mL, p=0.436), LV end-systolic volume (-13.0±20.8 vs. -13.7±24.9 mL, p=0.921), or LV ejection fraction (4.4±8.3 vs. 1.7±10.0%, p=0.347) between the patients with and without DRI aliskiren. Plasma renin activity in the DRI group was significantly lower in both the acute (0.2 [0.1 to 0.6] vs. 1.8 [0.7 to 7.6] ng/mL/hr, p<0.001) and chronic (0.5 [0.2 to 1.5] vs. 1.1 [0.6 to 3.2] ng/mL/hr, p=0.015) phases; however, aldosterone levels were significantly lower in the acute (38.1 [28.8 to 49.7] vs. 51.3 [36.9 to 108.0] pg/mL, p=0.025) but not the chronic (39.1 [23.0 to 66.0] vs. 55.7 [23.2 to 65.3] pg/mL, p=0.529) phase than in the non-DRI group.
Conclusions: Early administration of the DRI aliskiren add on conventional therapy, including an ACEI or an ARB, after primary AMI results in no attenuation of LVR.

P6443 | BEDSIDE
Spironolactone lowers the rate of repeat revascularization in acute myocardial infarction patients treated with percutaneous coronary intervention

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Purpose: We sought to assess the effect of the aldosterone receptor blocker, spironolactone, on 1-year clinical outcomes in all-comers with acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI).
Methods: A total of 10,309 AMI patients were recruited between November 2005 and April 2008 from a nationwide AMI registry. Patients were divided into two groups: those treated with spironolactone (n=720, 7.0%) and those who had not been treated at discharge. The primary endpoint was major adverse cardiac events (MACE), defined as the composite of death from any cause, recurrent AMI, or repeat revascularization at 1-year after admission.
Results: The spironolactone group had a greater number of co-morbidities than the non-spironolactone group. The mean follow-up duration of the overall study population was 313.4±119.9 days. After adjusting for potentially relevant variables including the propensity score, there was no significant association between the spironolactone treatment and MACE at 1 year (adjusted hazard ratio [HR]: 0.95, 95% confidence interval [CI]: 0.72-1.24, P=0.69) in the overall population. The risks of death from any cause, cardiac death, and recurrent AMI were also similar between the groups. However, patients who received spironolactone had a lower risk of repeat revascularization than those who did not receive spironolactone (adjusted HR: 0.58, 95% CI: 0.39-0.86, P=0.007). In subgroup analysis, the repeat revascularization rate was substantially lower in the spironolactone-treated group among patients with estimated creatinine clearance <60 (ml/min) and patients treated with drug-eluting sent, respectively. Of guideline-eligible patients (n=651/10,309, 6.3%), just 170/651 patients (20.7%) received a spironolactone at hospital discharge. The independent predictors of spironolactone prescription at discharge among guideline-eligible patients were Killip class ≥ II, admission glucose level (mg/dl), left ventricular ejection fraction (%), regional wall motion score >20, and multi-vessel coronary disease. When limited to the guideline-eligible patients' population, a statistical trend toward lower MACE was observed in patients treated with spironolactone (adjusted HR: 0.63, 95% CI: 0.37-1.10, P=0.10). Also, a trend of similar decline in the risk of repeat revascularization was seen in the spironolactone-treated group, as demonstrated in the whole population (adjusted HR: 0.47, 95% CI: 0.21-1.08, P=0.08).
Conclusions: All-comer AMI patients undergoing PCI who received spironolactone had a lower risk of repeat revascularization. Randomized trials are needed.

P6444 | BEDSIDE
Eicosapentaenoic acid treatment reduces acute inflammatory response and ventricular arrhythmias in patients with reperfused acute myocardial infarction

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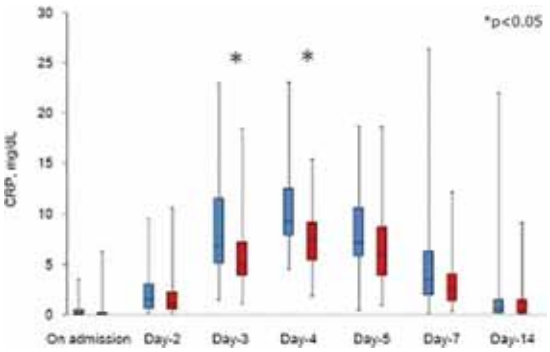
Background: Acute myocardial infarction triggers an inflammatory reaction, which plays an important role in myocardial injury. N-3 polyunsaturated fatty acid could attenuate inflammatory response by modulating several pathways.
Methods: This prospective, single-center randomized open-labeled trial consisted of 115 patients (70±13 years, 75% male) with acute myocardial infarction: ST-segment elevation myocardial infaction (STEMI), 95 patients and non-STEMI, 20 patients. They were randomized to the eicosapentaenoic acid (EPA) group (57 patients, EPA 1800 mg/day + pitavastaitn 2mg/day, orally) or the control group (58 patients, pitavastaitn 2mg/day alone, orally) just after successful percutaneous coronary intervention (PCI) and continued at least one month in the EPA group.
Results: Administration of EPA significantly reduced clinical adverse events until one month (10.5% vs. 29.3%, P=0.012), especially the incidence of malignant ventricular arrhythmias (7% vs. 20.6%, P=0.034). Peak C-reactive protein (CRP) value after PCI in the EPA group was significantly lower than in the control group (8.2 [5.6-10.2] mg/dl vs. 9.7 [7.6-13.9] mg/dl, P=0.0013). Multivariate analysis demonstrated that EPA use was an independent factor related to clinical adverse events until one month, along with peak CRP value.
Conclusions: EPA treatment in the acute stage of myocardial infarction reduced clinical adverse events including ventricular arrhythmias, accompanying by low-



CRP figure.

ering CRP value. Thus, EPA has anti-inflammatory and anti-arrhythmic effects in patients with reperfused acute myocardial infarction.

P6445 | BEDSIDE
Clinical outcomes of early initiation of pure eicosapentaenoic acid supplement after percutaneous coronary intervention in patients with acute coronary syndrome

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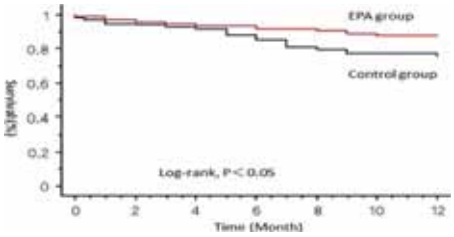
Purpose: Despite solid evidence of lower omega-3 fatty acids levels and cardiovascular death, benefits of supplemental omega-3 fatty acids on cardiovascular events remain controversial. The aim of this study was to evaluate whether early initiation of supplemental pure eicosapentaenoic acid (EPA) 1800 mg/day after successful percutaneous coronary intervention (PCI) can improve clinical outcome in patients with acute coronary syndrome.
Methods: A total of consecutive 203 patients (mean71 years, 75% male) with acute coronary syndrome including 66% of acute myocardial infarction were randomized to the EPA group (n=101, pure EPA 1800 mg/day + a statin) or the control group (n=102, a statin alone). Supplemental EPA was stared on the next day of PCI and continued until 12 months. The primary outcome measure was major adverse cardio- and cerebrovascular events (MACCE).
Results: There were no differences in baseline risk factors including levels of omega-3 fatty acids, PCI procedure, and max CK-MB between two groups. The incidence of MACCE in the EPA group (n=11) was significantly lower than that in the control group (n=22) ($p<0.05$). Cumulative event-free survival was significantly higher in the EPA group than in the control group (p=0.04; log-rank test). By adjusting for age, gender, conventional risk factors, and target vessel, EPA administration was identified as a good predictor of MACCE (hazard ratio;0.47, 95% CI 0.22 to 0.97, p=0.04).



Cumulative event-free survival curves.

Conclusion: Early loading of pure EPA after PCI therapy appears to confer improved one-year clinical outcomes in patients with acute coronary syndrome undergoing PCI. Our findings support the early initiation of omega-3 fatty acids after PCI as adjuvant therapy.

P6446 | BEDSIDE
Association of blood lipids, biomarkers of atherosclerosis and lipidtransport system genes polymorphism in patients with unstable angina

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Aim: To examine blood lipids, atherosclerosis biomarkers level and the carriage of "unfavorable" alleles of lipidtransport system genes polymorphisms in Uzbek patients with unstable angina (UA).
Material and methods: There were examined 125 Uzbek patients with UA. I group (n=63) consisted of patients with presence of coronary artery disease (CAD) in family history and II group (n=62) without family history of CAD. The control group consisted of 58 healthy persons. The G-A polymorphism of apolipoprotein A1 (apoA1), -516C/T polymorphism of apolipoprotein B (ApoB), ε2/ε3/ε4 polymorphism of apolipoprotein E (ApoE) and SstI polymorphism of apolipoprotein CIII (Apo CIII) genes was determined using reagents Diatom DNA Prep 200.
Results: In studying the distribution of "damaging" alleles among the patients with UA (n=125) in comparison with healthy persons, has been found a more prevalence of "A" allele carriers of the Apo A1 (HR 3,63, 95% CI 1,63-8,04, P=0,002). The distribution of "damaging" alleles in comparative analysis of the II group with healthy persons did not differ significantly, whereas in I group had significantly greater accumulation of alleles: "A" G-A polymorphism of Apo A1 gene (HR 5,99, 95% CI 2,52-14,24, P=0,001), "ε4" polymorphism of Apo E gene (HR 2,91, 95%, CI 1,12-7,62 P=0,044). At ε4-carriers were higher LDL cholesterol level ($P<0,001$), Apo B/ Apo A ratio ($P<0,01$) and high-sensitive C-reactive protein level ($P<0,01$), whereas "A" (M1-) carriage are accompanied by decrease HDL cholesterol level ($P<0,005$).
Conclusion: Among Uzbek patients with unstable angina and family history of coronary artery disease accumulation of "damaging" alleles were observed: "ε4" of Apo E and "A" (M1-) G-A polymorphism of Apo A1 genes, which were associated with lipid and biomarkers disorders.

P6447 | SPOTLIGHT
Relationship between total and high weight molecular adiponectin and culprit lesion components in patients with unstable coronary artery disease

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The present study investigated the relationship among serum total and high weight molecular adiponectin (HWM-adiponectin) and culprit leisure components in patients with unstable coronary artery disease. Previous studies showed a pivotal role of anti-atherogenic and cardiovascular protection of adiponectin. However, the relationship between adiponectin, especially HWM-adiponectin and plaque characters was still unknown. 60 patients with unstable coronary artery disease were included in our study. We used ELISA to analyze the concentration of total and high weight moleculer adiponectin. Culprit lesion was identified by analyzing ST-T alternation on electrocardiograms,left ventricular wall motion abnormalities, angiographic complex lesions and IVUS-detected plaque rupture.We performed Virtual Histology-Intravascular Ultrasound examination on each culprit lesion and analyzed the relationship between the total and high weight molecular adiponectin and the culprit lesion components. HWM-adiponectin is positively associated with the absolute volume of fibro-fatty ($r=0.505$, $P<0.01$) and fiber ($r=0.499$, $P<0.01$) respectively.While the concentration of the total and high weight molecular adiponectin increases in patients with unstable coronary artery disease, the relatively stable plaque composition of the culprit leision is growing.

P6448 | BEDSIDE
Blockade of platelet alpha2B-adrenergic receptors in patients with coronary artery disease: A novel antiaggregant mechanism

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Purpose: Platelets play a vital role in hemostasis and thrombosis. Catecholamines have a profound effect on platelet aggregation and atherothrombosis but the exact mechanism involved is insufficiently understood. In this report, we demonstrate the existence and role of alpha2B–adrenergic receptors (α2B–ARs) in platelets from patients with coronary artery disease (CAD) compared to normal individuals.
Methods: Twenty patients with CAD who were under dual antiplatelet therapy with clopidogrel 75 mg and acetylsalicylic acid 100 mg and 20 healthy individuals were included. Blood samples were obtained from which platelets were isolated. The α2B-ARs gene expression in platelets was examined by real time PCR. In order to investigate their function, we performed light transmittance aggregometry by examining the inhibitory effects of specific α2B-AR antibodies.
Results: Patients with CAD showed a significantly reduced expression of the receptor in the platelets (132.6±90.8 in normals versus 42.1±14.7, p=0.001). Notably, pretreatment with α2B –Abs resulted in a significant further reduction of platelet aggregation. The ADP-treated plasma showed a significant reduction in platelet aggregation after pre-treatment with α2B-Abs (47±5.8% for the control group versus 30.7±2.9% for the group with α2B-Abs pretreatment, $p<0.001$). When arachidonic acid was used to induce aggregation, pre-treatment with α2B -Abs reduced platelet aggregation from 47.2±9.3% to 27.7±7.9%, p=0.006). Similarly, the presence of α2B-Abs decreased platelet aggregation induced by epinephrine from 34.2±12.1% to 11.1±7.2% (p=0.02).
Conclusions: Patients with CAD showed reduced platelets α2B-ARs gene expression compared to healthy individuals. Inhibition of α2B-ARs in platelets may offer a novel therapeutic opportunity in the prevention of atherothrombotic events. Interestingly, even in patients with coronary artery disease who were receiving dual antiplatelet therapy with aspirin and clopidogrel, the inhibition of α2B-ARs had an additional antiaggregant effect.

RISK FACTORS AND CORONARY ARTERY DISEASES

P6450 | BEDSIDE
Increased risk of coronary heart disease in patients with chronic osteomyelitis: a population-based study in a cohort of 23 million

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Objectives: Chronic inflammatory disease may trigger vascular atherosclerosis. This study aimed to determine whether chronic osteomyelitis (COM) is linked to an increased risk of coronary heart disease (CHD).
Methods: A national insurance claim dataset of more than 23 million enrollees was used to identify 15,054 patients with COM and 60,216 randomly selected age- and gender-matched controls between 2001 and 2009 for comparing the risk and incidence of CHD. The study period was from the entry date to the first date of the following events: the diagnosis of CHD, death, withdrawal from the Taiwan National Health Insurance program or the end of 2010. The analysis of the CHD risk was performed using Cox proportional hazards regression model.
Results: During a follow-up period of 67,927 person-years, the overall incidence rate of CHD in COM cohort was 1.95-times higher than non-COM cohort (16.66 vs. 8.52 per 1000 person-years). After controlling age, gender and four co-morbidities (hypertension, diabetes, hyperlipidemia, and stroke), the risk remained significantly higher in the COM cohort than the control group (adjusted hazard ratio [HR] =1.65, 95% confidence interval [CI] =1.54-1.78, $p<0.001$). In age-stratification analysis, the younger population carried higher CHD risk than the elderly (from HR =3.42, 95% CI =1.60-7.32 in age <35 to HR =1.39, 95% CI =1.15-1.68 in age ≥80).
Conclusions: This study demonstrates for the first time that COM is an independent risk factor for CHD, particularly in the younger population. Further studies are necessary to explore the underlying mechanisms linking COM and CHD.

P6451 | BEDSIDE
Parathyroid hormone is associated with cardiovascular mortality in patients with acute coronary syndrome

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Purpose: Parathyroid hormone (PTH) has been linked to endothelial dysfunction, elevated pulse pressure, increased carotid artery intima-media thickness and vascular calcification. Elevated PTH levels in terms of secondary hyperparathyroidism have been found in patients with chronic kidney disease. Studies evaluating the relationship between PTH and risk of cardiovascular mortality in patients with normal kidney function are, however, sparse. We therefore aimed to evaluate the relationship between PTH and long term CV mortality in patients with acute coronary syndrome (ACS).
Methods: A total of 1036 patients with ACS and measurement of PTH at baseline were included in the analyses. Data was extracted from the LUdwigshafen RIsk and Cardiovascular Health (LURIC) study (1997–2000). Serum PTH was measured by an ElectroChemiLuminescence Immunoassay (ECLIA) on an Elecsys2010. Statistical models were carefully evaluated for normal distribution (including log-transformation, where appropriate), collinearity and residuals.
Results: Patients (age: 63.7±10.4years; 51.2% females, median follow up: 9.9years) had reasonable CAD burden with 24.5% one-, 26.5% two- and 40.4% multi-vessel disease (a stenosis of 50% or greater was considered significant). In Cox proportional hazard analysis (with backward elimination procedure) adjusted for age, sex, systolic blood pressure, waist to hip ratio log, diabetes, active smoking, eGFR-MDRD, left-ventricular function, extent of CAD and LDL-C, PTH was significantly associated with increased CV mortality (P=0.007; HR 2.67, 95%CI 1.30-5.47). Further adjustments for HDL, resting heart rate log, beta-blockers, calcium antagonists, statins, oral anticoagulation and physical activity as well as the exclusion of patients with severe chronic-kidney disease (CKD) stages 4-5 (n=269; mean eGFR: 23.6±7.2ml/min/1,73m^2) did not materially change this association (P=0.045; HR 2.30, 95%CI 1.02-5.18).
Conclusions: In patients with ACS, PTH is strongly related to CV mortality, independent of kidney function. Mechanistic approaches are warranted to elucidate mechanisms of PTH interfering treatment strategies in patients at CVD risk.

P6452 | BEDSIDE
Euro-CCAD: Differing conventional atherosclerosis risk factors for coronary calcification depending on degree of luminal stenosis

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Background and aim: Conventional atherosclerosis risk factors are well established precursors for the development of acute coronary syndromes, although their individual and cumulative relationship with coronary stenosis and calcification remains not fully determined. The aim of this study was to assess the impact of conventional risk factors; hypertension, diabetes, hypercholesterolemia, obesity, family history and smoking on the severity of coronary artery calcification (CAC) and significant (>50%) luminal stenosis in 6,300 symptomatic patients from Sweden, Denmark, Germany, France, Italy, Spain and USA.
Methods: Patients' mean age was 60.2±11.7 years, 48% females and none had prior coronary intervention or acute coronary syndrome. All patients underwent coronary calcium scoring by Agatston method followed by coronary angiography to exclude significant (>50%) luminal stenosis.
Results: There was a close relationship between the cumulative risk factors and the overall CAC score ($p<0.001$), with males having more risk factors than females, (3.50±1.50 vs. 2.29±1.40, $p<0.0001$). In patients with significant coronary stenosis, the independent predictors of severe CAC (score >400) were diabetes (OR=1.58, $p<0.0001$) and hypertension (OR=1.35, $p<0.0001$), while the risk factors in patients with no significant luminal stenosis were diabetes (OR=2.26, $p<0.0001$), hypercholesterolemia (OR=1.23, p=0.03) and smoking (OR=1.27, p=0.03). The same risk factors also predicted extensive CAC (score >1000).
Conclusion: Although coronary calcification is generally considered a manifestation of atherosclerosis, the impact of conventional risk factors on its formation differs in patients with and without significant luminal stenosis.

P6453 | BEDSIDE
Epicardial adipose tissue thickness correlates with the presence and severity of angiographic coronary artery disease

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Purpose: Epicardial adipose tissue (EAT) is suggested to correlate with metabolic risk factors and to promote plaque development in the coronary arteries. We sought to determine whether EAT thickness was associated or not with the presence and extent of angiographic coronary artery disease (CAD)
Methods: We measured epicardial fat thickness by computed tomography and assessed the presence and extent of CAD by coronary angiography in participants from the prospective EVASCAN study. The association of EAT thickness with cardiovascular risk factors, coronary artery calcification scoring and angiographic CAD was assessed using multivariate regression analysis.
Results: Of 970 patients (age 60.9±11years, 71% male), 75% (n=731) had CAD. Patients with angiographic CAD had thicker EAT on the left ventricle lateral wall (LVLW) when compared with patients without CAD (2.74±2.4mm vs. 2.08±2.1mm; p=0.0001). By receiver operating characteristic curve analysis, an EAT value ≥2.8 mm on the LVLW best predicted the presence of significant (>50% diameter) coronary artery stenosis. Sensitivity was 46.1% and specificity was 66.5%. The odds ratio (OR) for a patient with a LVLW EAT value ≥2.8 mm to have CAD was 1.67 (95%CI [1.23-2.26]) and this relation remained significant after adjusting for CAD risk factors (OR=1.45 [1.02–2.06]; p=0.0362).
Increased LVLW EAT thickness correlated positively with the extent of CAD: LVLW EAT thickness mean was 2.08±2.1mm for the patients with no or minimal vessel disease, 2.43±2.4mm for the patients with single vessel disease, 2.65±2.2mm for patients with 2 vessel disease or left main disease and 2.95±2.5mm for patients with 3 vessels disease (p for trend=0.0001)
Conclusion: Although left ventricle lateral wall EAT thickness correlated with the presence and extent of angiographic CAD, independently of traditional cardiovascular ris factors, it is probably of little value as a diagnostic or screening tool since other methods such as calcium scoring have far superior sensibility and specificity.

P6454 | BEDSIDE
Association of A603G tissue factor gene polymorphism with endothelial dysfunction and carotid arteries remodeling in coronary artery disease patients

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The actual problem in clinical cardiology is the investigation of genetic factors, associated with vascular remodeling and endothelial dysfunction in patients with coronary artery disease (CAD). Some experimental data have shown that tissue factor integrates procoagulant and proinflammatory reactions in vessel wall.
Purpose: To access the association of A603G tissue factor (TF) gene polymorphism with markers of endothelial dysfunction and carotid arteries remodeling in CAD patients.
Methods: The A603G TF gene genotypes were determined in a sample of 212 men with CAD and 55 healthy men by a polymerase chain reaction-

restriction length polymorphism (PCR-RFLP)-based method. Vascular cell adhesion molecule-1 (VCAM-1), IL-8, IF-gamma, IL-10 plasma levels were studied by ELISA. Gomocystein content was examined by liquid chromatography (Aligent 1100). Dopplerography of carotid arteries was performed. ANOVa analysis, exact Fisher test and Odds-Ratio calculation were performed.
Results: The frequency of G603G genotype in CAD patients was higher than in the group of healthy people (72 from 212 and 11 from 55, p=0,017). IL-8 content in CAD patients with G603G tissue factor gene genotype were higher, than in A603A genotype carriers (981,3±214 pcg/ml and 308,1±59,2 pcg/ml respectively, p<0,05). The same tendencies were revealed in interferon-gamma plasma content (1,58±0,251 pcg/ml in G603G TF gene genotype carriers and 0,99±0,205 pcg/ml in A603A genotype carriers. No significant difference in IL-10 plasma content in patients-carriers of different tissue factor gene genotypes was found. The CAD patients - carriers of G603G genotype had hyperhomocysteinemia (15,1±0,85 mcmol/l and 12,1±0,69 mcmol/l in healthy people respectively, p<0,05). Intima-media complex in CAD patients-carriers of G603G TF gene genotype was higher, than in patients – carriers A603A genotype: 1,18±0,023mm and 0,87±0,016 respectively.
Conclusions: Our study have revealed the association of G603G tissue factor gene genotype with elevated markers of endothelial dysfunction, hyperhomocysteinemia and intima-media thickening of carotid arteries in coronary artery disease patients.

P6455 | BEDSIDE
Body mass index and acute coronary syndromes: paradox or confusion?

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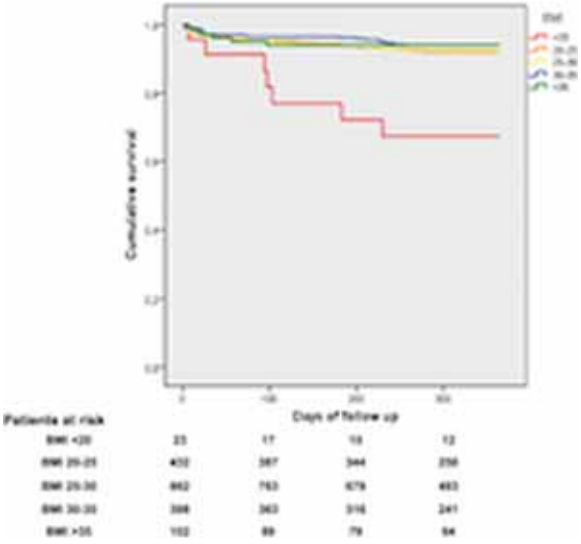
Objectives: A better prognosis in obese patients has been described in acute coronary syndromes (ACS). However, this evidence is mostly based on retrospective studies and has provided conflicting results. No study reported cause specific mortality according to body mass index (BMI) in ACS. We aimed to prospectively assess the impact of BMI on mortality and its specific causes in ACS patients.
Methods: We prospectively included non-selected ACS patients admitted in a tertiary care Coronary Unit, collecting baseline characteristics, management and clinical course. Patients were stratified into five clinically meaningful BMI subgroups (<20, 20-25, 25-30, 30-35, >35 kg/m^2). The primary outcome was midterm mortality, its causes and its association with BMI. This association was assessed by the Cox regression method.
Results: We included 2040 patients. Mean age was 62.1 years. Low weight patients (BMI <20) were older, with less cardiovascular risk factors, higher prevalence of chronic obstructive pulmonary disease and worse renal function.
Mean follow up was 334 days. The unadjusted analysis showed lower all-cause mortality in all subgroups as compared to low weight patients. After adjusting for potential confounders, this association remained significant for patients with BMI 20-25. Cardiac mortality was similar across BMI subgroups. In contrast, the adjusted analysis showed a significanty lower non-cardiac mortality in patients with BMI 20-25, 25-30 and 30-35 as compared to low weight patients.



Conclusions: Baseline characteristics in ACS patients significantly differ according to their BMI status. The prognostic impact of BMI seems mostly related to extracardiac causes in low weight patients.

P6456 | BEDSIDE
Does subclinical renal dysfunction have prognostic implications among acute coronary syndrome patients with normal serum creatinine?

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Background: Severe renal dysfunction is an important predictor of adverse events in acute coronary syndromes (ACS). The serum creatinine value per se is a poor indicator of renal function and patients with normal serum creatinine (NSC) may have insidious renal dysfunction; hence renal function should be evaluated by estimating glomerular filtration rate (GFR) using MDRD or Cockcroft-Gault formulas.
Aim: To clarify if mild renal dysfunction (GFR 60-89 ml/min) has any influence on the prognosis of ACS patients with NSC.
Methods: We analysed 4420 consecutive patients who were admitted to our coronary care unit with ACS and included in a prospective registry, from Jan 2003 to Oct 2013. Patients with NSC (≤1.3mg/dl) on admission were selected (86.4%, n=3820) and grouped according to estimated GFR, calculated by MDRD formula: group 1 [GFR>90 ml/min (n=1778;46,5%)]; group 2 [GFR 60-89 ml/min (n=1681;44%)] and group 3 [TFG 30-59 ml/min (n=361;9,5%)]; none of the patients had GFR <30 ml/min. We compared the clinical and laboratory features, treatment and adverse events for each group. The primary endpoint was the occurrence of death at 6 months; follow-up was completed in 95% of patients.
Results: Patients in group 3 were older (57±12 vs 66±12 vs 74±9 years; p<0.001) and more frequently women (15.7 vs 23.6 vs 71.5%; p<0.001). They also had a more frequent history of hypertension (52.8 vs 65.4 vs 77%; p<0.001), diabetes (21.1 vs 25.2 vs 39.1%; p<0.001) and previous acute myocardial infarction (11.6 vs 16.2 vs 22.4%; p<0.001), angina (12.4 vs 18.1 vs 20.5%; p<0.001) and stroke (3.7 vs 6.9 vs 10.8%; p<0.001). On admission, they more often presented with Killip class >1 (9.5 vs 22.1 vs 38.1%; p<0.001) and anaemia (12.9 vs 19.4 vs 36.4%; p<0.001), but had less often ST-segment elevation ACS (51.9 vs 49.8 vs 39.7%; p<0.001). Patients in group 3 underwent percutaneous coronary intervention less frequently (51.3 vs 49.4 vs 32.6%; p<0.001). There was a progressive increase in in-hospital (0.7 vs 3.4 vs 9.2%; p<0.001) and 6-month mortality (2.7 vs 8.0 vs 22.8%; p<0.001) as GFR decreased. In multivariate analysis, not only GFR 30-59 ml/min [adjusted OR 3.33; 95% CI (1.40-3.51),p<0.001], but also GFR 60-89 ml/min remained as an independent predictor of 6-month mortality [adjusted OR 2.22; 95% CI (1.40-3.51),p<0.001].
Conclusion: In patients admitted with ACS and NSC it is important to calculate their GFR, as more than half have mild or moderate renal dysfunction, which has prognostic relevance. Even mild renal dysfunction (GFR 60-89 ml/min) is a strong independent predictor of mortality in ACS patients with normal serum creatinine.

P6457 | BEDSIDE
Gender differences affecting outcome in young patients (<55y) with acute coronary syndromes

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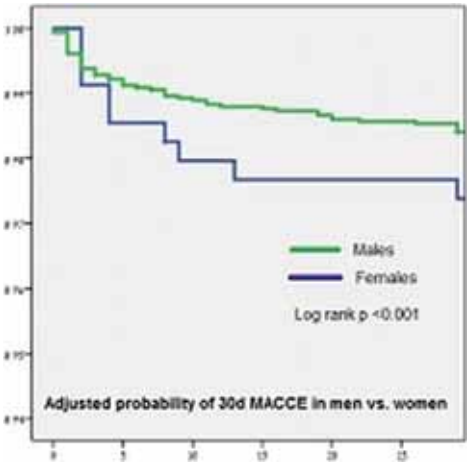
Background: Women are usually protected against coronary artery disease due to hormonal and risk-factor profile. Previous studies have suggested a worse outcome in women hospitalized with ACS as compared to men. ACSIS registries have shown 3-fold higher mortality rates among women after ACS. However, when adjusted to age this difference does not exist. We aimed to compare the risk-profile and outcome between young (≤55y) women and men admitted with ACS.
Methods: We analyzed clinical characteristics, management strategies, and out-



comes of man and women, 55 years old or younger enrolled in the Acute Coronary Syndrome Israeli Survey (ACSIS) 2000-2010.
Results: Among 11,536 patients enrolled, 3424 (30%) were <55y old (342 women and 3082 men). Women suffered more from diabetes mellitus and hypertension (p<0.001 for both) despite a similar age (48.7±5.7 vs. 48.3±5.6, p=0.29). Women presented less often with STEMI (50% vs. 57%, p=0.007) or with typical chest pain (73% vs. 80%, p=0.004), and had higher rates of GRACE score≥140 (19% vs. 12%, p=0.007). After adjustment for GRACE score, diabetes and enrollment year, women had a lower likelihood to receive PCI during hospitalization (OR 0.6, p=0.007). Female sex was not associated with higher risk for 7d and 1y mortality. It was, however, an independent risk factor for 30d MACCE (OR 1.9, p=0.005) (Figure).
Conclusions: In young patients admitted with ACS, women are a unique high-risk group that presents a diagnostic challenge for clinicians. Women receive less invasive therapy during hospitalization and have more short-term adverse events.

P6458 | BEDSIDE
Relationship of carotid plaque area to the severity of coronary artery obstructive disease

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Purpose: Several studies reported that the carotid intima-media thickness (IMT) as a week predictor of coronary artery disease. Contrary, there are little available data regarding the plaque area and severity of coronary artery obstructive disease (CAOD). In this study, we evaluated the relationship of carotid plaque area with severity of CAOD in the patients of acute coronary syndrome
Methods: We retrospectively reviewed medical records of the patients who performed coronary angiography (CAG), carotid ultrasound and transthoracic echocardiography within 6 months interval. Total 101 patients were analyzed in this study. More than 50% luminal narrowing of CAG was regarded coronary artery obstructive disease (CAOD). Plaque area was measured in magnified longitudinal views of each plaque seen in left and right common, internal and external carotids arteries. The sum of all plaques seen between the clavicle and angle of the jaw was defined total plaque area.
Results: Mean age of total subject was 60.0±12.8. Female proportion was 23.8% (n=24). Medical history of hypertension was in 39 (38.6%) and diabetes mellitus was in 23 (22.8%). The CAG results was as followings; one vessel CAOD in 55 (54.5%), two vessels CAOD in 30 (29.7%) and three vessels CAOD in 16 (15.8%). ST elevation myocardial infarction was the most frequent clinical diagnosis in 66 (65.3%) and followed by unstable angina in 18 (17.8%) and non ST elevation myocardial infarction in 17 (16.8%). Average carotid IMT was 0.82±0.26 mm and total plaque area was 7.7±10.7 mm^2. Average left ventricular mass index (LVMi) was 98.6±22.2 g/m^2 and ejection fraction was 55.2±11.8%. Multi-vessel CAOD related older age (one vessel vs. three vessel; 58.6±12.3 vs. 66.3±16.8, p=0.026). Multi-vessel CAOD showed positive correlation of increased average IMT (one vessel vs. three vessel; 0.79±0.22 vs. 0.97±0.36 mm, p=0.045) and increased total plaque area (5.2±7.8 vs. 20.0±17.5 mm^2, p<0.001). After adjusted covariate (age, sex, serum creatinine, hypertension, diabetes mellitus and calcification of carotid artery), the plaque area showed positive correlation with severity of CAOD; CAOD=1.29+0.024 (plaque area) +0.409 (diabetes mellitus).
Conclusions: The carotid plaque area is more powerful than carotid IMT and carotid artery calcification for predict severity of CAOD. The impact of concerning carotid total plaque area on cardiovascular outcome in acute coronary syndrome needs to be investigated.

P6459 | BEDSIDE
The impact of polyvascular atherosclerotic disease for the long-term outcome of patients undergoing percutaneous coronary intervention

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Purpose: The aim of this study was to investigate the long-term outcome following percutaneous coronary intervention (PCI) for patients with polyvascular disease (polyVD) such as peripheral artery disease (PAD), renal artery stenosis (RAS), internal carotid artery stenosis (ICS) and abdominal aortic aneurysm (AAA).
Methods: A total of 2052consecutive patients underwent PCI were prospectively enrolled between November 2007 and October 2009. Among them, 534cases were detected polyVD by ultrasound and ankle-brachial index; PAD were in 367cases (17.9%), ICS in 95cases (4.6%), RAS in 94cases (4.6%), and AAA in 116cases (5.7%). We evaluated the incidence of cardiovascular (CV) death as primary outcome, and also investigated the incidence of myocardial infarction (MI), stroke, target lesion revascularization (TLR) and major adverse cardiac events (MACE; included of death, MI, stroke) as secondary outcome.
Results: The mean follow-up term was 3.5±1.1years. In the polyVD group, the incidence of CV death was significantly higher than in the only coronary artery disease (CAD) group (P<0.0001). Similarly, the incidence of MI, stroke and MACE was significantly higher in the polyVD group than in the only CAD group (polyVD 3.3% vs CAD 1.9% at 3years, P=0.006; polyVD 6.6% vs CAD 1.4% at 3 years, P<0.0001; and polyVD 22.6% vs CAD 7.9% at 3 years, P<0.0001, respectively). Only the TLR rate was similar between the two groups (polyVD 20.7% vs CAD 22.2% at 3 years, P=0.86). Age >75 years old, hemodialysis, history of CABG,thicker IMT>1.30mm, lower ABI <0.94 were found to be independent predictors of cardiovascular death.

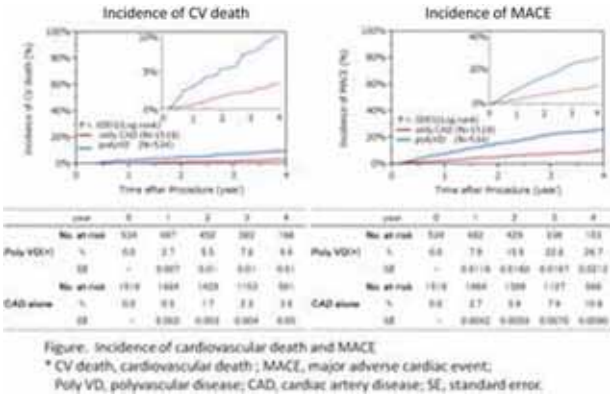

Figure. Incidence of cardiovascular death and MACE
* CV death, cardiovascular death ; MACE, major adverse cardiac event;
Poly VD, polyvascular disease; CAD, cardiac artery disease; SE, standard error.

Incidenceof CV death and MACE.

Conclusion: The incidence of CV death, MACE, MI, stroke after successful PCI was significantly higher in patients with polyVD than with only CAD.

P6460 | BEDSIDE
Temporal trends in major risk factors and in-hospital mortality over two decades in patients with first acute myocardial infarction: a study from a 20 years registry in a middle-eastern country

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Background and purpose: Has the risk profile in patients with Acute Myocardial Infarction (AMI) changed over the years?. We analyzed a 20 years registry of all ACS patients to study the changes in the temporal trends of major Cardiovascular Risk Factors (CVRFs), as well as age, gender and in-hospital mortality over 2 decades among patients with "First" AMI in a middle-eastern country.
Methods: All patients hospitalized with first AMI in 20 years (January 1991 to December 2010) were included. Changes in age, gender and major CVRFs (Hypertension, Diabetes, Smoking, Dyslipidemia, and Family History of premature coronary artery disease (CAD) were analyzed along with related in-hospital mortality. All changes were contrasted in two consecutive decades.
Results: Out of 12,881 AMI Patients, 10,915 patients were admitted with "first" AMI. Comparing the two decades, the proportion of first AMI of the total cardiac hospitalizations increased from 34% to 66%, a relative increase of 48%. Comparing the two decades, the proportion of STEMI decreased from 69.7% in first decade to 54% in second decade (p<0.001). Conversely N-STEMI increased from 30% to 45.2% (p<0.001). The over all mean age increased from 51±12 to 54±12 years (p<0.05) and for both men (50±11 to 52±11, p<0.001) and (61±12 to 63±12 for women, p<0.001). Furthermore, there was a significant shift in the age of first AMI, with an ever increasing proportion for middle age (51-70 years) from 1510 (40%) to 3429 (48%, p<0.001), as well as in the elderly (>70 years) from 6.0% to 9.0% of all first AMI patients (p<0.001). While history of Dyslipidemia declined from 26% to 18% (p<0.001), the rate of all other risk factors increased significantly, thus hypertension increased from 24% to 40%, diabetes from 31% to 41% and smoking increased from 29% to 42% (p<0.001 for all) (Table 1). Family history of premature CAD did not change (p<0.34), but the overall in-hospital mortality decrease 8.8% to 5.4%, p<0.001 over the study period. Multivariate logistic regression analysis showed that in both decades, age (adjusted OR 3.80, 95% CI 2.97-4.84, p<0.001), female gender (adjusted OR 1.98, 95% CI 1.62-2.42, p<0.001) and Diabetes were independent predictors of in-hospital mortality (adjusted OR 1.60, 95% CI 1.35-1.90, p<0.001).
Conclusions: This large registry suggests a steady increase in the burden of major risk factors. Although the age at first AMI is getting older and in-hospital mortality lower, the rising trend in the risk profile may prelude to a forthcoming epidemic of coronary events. It calls for more effective efforts to reverse the trend in the population of the Middle East.

P6461 | BEDSIDE
Course of depressive status and risk of coronary heart disease and stroke over 10 years in older adults. A prospective observational study cohort. The Three-City study

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Objective: To prospectively investigate the association between cumulative de-

pressive symptoms (DS) over time and coronary heart disease (CHD) and stroke events in older adults.
Setting: The Three City Study is a multisite community-based prospective cohort.
Participants: The study population includes 7313 men and women aged 65 years and over with no history of CHD, stroke or dementia. A score ≥16 on the 20-item Center for Epidemiologic Studies Depression Scale questionnaire defined the presence of DS at baseline and during follow-up visits. At each date of an event, the risk of vascular events associated with the number of DS episodes over time was calculated using Cox proportional hazard model with time dependent variable.
Results: DS were present in respectively 22.7%, 19.5%, 19.8% and 21.7% of the participants at baseline, 2, 4 and 7 years of follow-up. The corresponding rates for antidepressants use were 6.7%, 7.2%, 8.1%, 8.0%. After a median follow-up of 8.4 years (SD 2.3years), 629 first CHD or stroke events (124 fatal) were adjudicated, including 384 first CHD and 245 first stroke. After adjustment for study centre, sociodemographic characteristics and baseline vascular risk factors, there was a significant 1.15 increased risk of CHD and stroke for each additional episode of DS (95%CI: 1.06–1.25). Associations were similar for CHD, stroke and non fatal events, and was stronger for fatal CHD or stroke events (HR=1.28; 95% CI: 1.09-1.51). Analysis restricted to participants free of disability or free of antidepressants at baseline but adjusting for these incident variables virtually unchanged the results.
Conclusion: The current data support a progressively increased risk of CHD and stroke events with the number of DS episodes over time in older adults, independently of major vascular risk factors, disability and antidepressants use.

ANTIPLATELET THERAPY IN ACUTE CORONARY SYNDROME PATIENTS

P6463 | BEDSIDE
Serial measurements of platelet reactivity during one year of clopidogrel or ticagrelor treatment in patients presenting with ST-segment elevation myocardial infarction - the TOPS study

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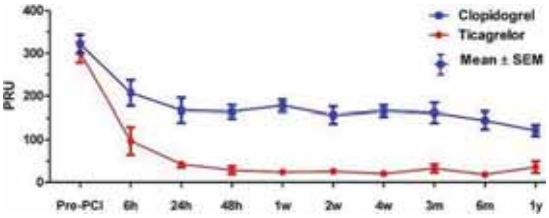
Purpose: Inhibition of platelet reactivity by dual antiplatelet therapy (DAPT) is essential to reduce the risk for atherothrombotic events in patients presenting with a STEMI who are treated with primary PCI. However, it is unknown whether platelet reactivity on this treatment remains stable over time. We evaluated platelet reactivity with various platelet function tests during one year of clopidogrel or ticagrelor treatment in STEMI patients undergoing PCI to determine if and when a stable level of platelet reactivity is reached.
Methods: The TOPS study is a non-randomized, open label and single centre study. Patients undergoing primary PCI with stenting for STEMI who received a loading dose (LD) of DAPT before PCI (500mg Aspegic iv plus 600mg clopidogrel or 180mg ticagrelor), followed by standard maintenance doses were included. Platelet reactivity was measured with the VerifyNow P2Y12 assay, Light Transmittance Aggregometry (LTA; 20μmol/L ADP), and Multiplate (MEA; ADP 6.5μmol/L) directly before PCI, and at 6, 24 and 48 hours, 1, 2 and 4 weeks, and 3, 6, and 12 months after LD.
Results: A total of 33 patients were included. As measured with the VerifyNow, platelet reactivity was inhibited after 24 hours after LD to a level which remained stable until 1 year of follow-up, both for clopidogrel and ticagrelor (see figure). LTA and MEA both showed comparable results; platelet reactivity was inhibited to a stable level 6 hours after LD until 1 year of follow-up.



Serial measurements with VerifyNow P2Y12.

Conclusion: In STEMI patients undergoing primary PCI, treated with DAPT, platelet reactivity is reduced to a stable level of platelet reactivity up to 1 year of follow-up from 24 hours and 6 hours after LD measured, respectively, with VerifyNow or LTA and MEA. These time points can guide the performance of platelet function testing.

P6464 | BEDSIDE
Prasugrel versus ticagrelor in acute coronary syndrome: a randomized comparison

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Purpose: European guidelines recommended the use of Prasugrel or Ticagrelor in ACS patients as first choice. The present biological study was designed to compare the effectiveness and safety of Prasugrel versus Ticagrelor in patients undergoing PCI for ACS.
Methods: In this randomized study, consecutive patients admitted for ACS in our institution were assigned to receive a loading dose of Prasugrel 60 mg or Ticagrelor 180 mg and were treated at discharge with Prasugrel 10 mg once a day or Ticagrelor 90mg twice a day. Antiplatelet response was assessed one month after ACS with Platelet Reactivity Index VASP (PRI VASP) and ADP-induced platelet aggregation (%ADP). LTPR was by PRI VASP≤20%. Primary end point was the comparison of degree of platelet inhibition and incidence of LTPR in patients treated with Ticagrelor or Prasugrel, one month after an ACS.
Results: Between March and June 2013, 96 patients (48 in each arm) were randomly assigned to Prasugrel or Ticagrelor for ACS. We observed 14% of bleeding complications (n=13 patients), 8 in the Ticagrelor cohort versus 5 in the Prasugrel therapy group. At one month, PRI VASP (20.2±9.9% vs. 25.8±11.5% p=0.01) and %ADP (37.9±10.3% vs. 48.9±10.8% p<0.01) were significantly lower under Ticagrelor therapy than under Prasugrel therapy. We observed LTPR status in 33% of the patients under Prasugrel and in 58% under Ticagrelor (p=0.01). Interestingly there was a trend in favor of an increased bleeding risk at one month on Ticagrelor (17% vs. 10% p=0.15).

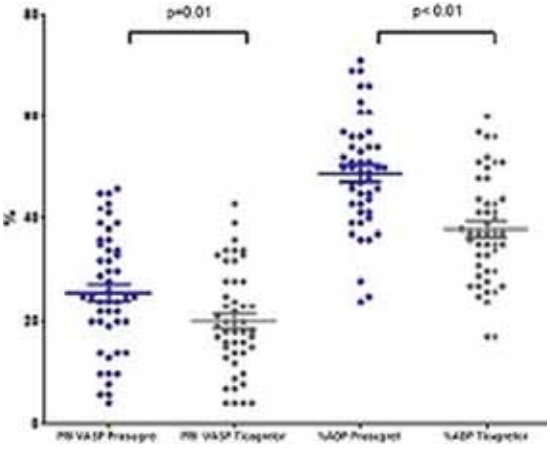

Figure 1

Conclusions: The present study suggests that Ticagrelor is associated with higher platelet inhibition and higher incidence of "hyper response" than Prasugrel one month after ACS, possibly exposing patients to higher risk of bleeding complications.

P6465 | BEDSIDE
Duration of dual antiplatelet therapy and clinical outcomes after drug-eluting stent implantation in patients presenting with acute coronary syndrome

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Purpose: Although prolonged dual antiplatelet therapy (DAPT) is recommended longer than 1 year in patients with acute coronary syndromes (ACS), the optimal duration of DAPT remains controversial in patients with ACS undergoing percutaneous coronary intervention (PCI) with drug-eluting stents (DES). In the present study, we compared long-term clinical outcomes after zotarolimus-eluting stent (ZES) implantation between ACS patients who received DAPT for up to 6 months only and those treated for longer than 6 months.
Methods: From a multicenter registry of consecutive patients treated with ZES, 1740 patients with ACS were selected for this analysis. Landmark analyses were performed among patients who were alive and remained event free from myocardial infarction (MI), repeat revascularization, stent thrombosis, and stroke at 6 months follow-up.
The primary outcome was major adverse cardiac and cerebrovascular events (MACCE), defined as a composite of all-cause death, MI, target vessel revascularization (TVR), stent thrombosis, or stroke.
Results: The median follow-up duration was 22.5 months. Among patients who

were event free at 6 months (n=1674), the rates of MACCE was 6.4% in patients with DAPT >6 months (n=1140) and 4.7% in patients with DAPT ≤6 months (n=534) (adjusted hazard ratio [HR] 0.95; 95% confidence interval [CI] 0.55-1.65; P=0.86). The rates of all-cause death (adjusted HR 1.55, 95% CI 0.19-12.69, P=0.68), MI (adjusted HR 0.99, 95% CI 0.11-9.11, P=0.99), target lesion revascularization (adjusted HR 1.04, 95% CI 0.57-1.91, P=0.89), TVR (adjusted HR 1.09, 95% CI 0.65-1.85, P=0.74), stent thrombosis (adjusted HR 0.28, 95% CI 0.2-4.89, P=0.38), and stroke (adjusted HR 0.23, 95% CI 0.02-3.43, P=0.29) did not differ significantly between the 2 groups. After propensity-score matching (n=469 pair), DAPT >6 months was not associated with a lower incidence of MACCE compared with DAPT ≤6 months (adjusted HR 0.80, 95% CI 0.44-1.45, P=0.46). These results were also consistent across various subgroups. Among patients with prior stroke, however, MACCE occurred less frequently in patients taking DAPT for more than 6 months as compared with patients taking DAPT for up to 6 months, although interaction test did not reach statistical significance (interaction P value=0.08).
Conclusions: DAPT beyond 6 months does not seem to reduce the risk of MACCE in patients with ACS undergoing PCI with ZES. However, it should be needed to confirm this finding in larger and randomized studies.

P6466 | BENCH
Platelet microRNA-15b protects against high on-treatment platelet reactivity in patients with acute coronary syndromes through bcl-2-mediated platelet apoptosis

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Purpose: To explore the association between platelet microRNAs (miRNAs) and interindividual variability of on-treatment platelet reactivity in patients with acute coronary syndromes (ACS), and to address the molecular mechanisms underlying the modulation of miRNAs in platelets.
Methods: In a cohort of 208 patients with ACS on dual antiplatelet therapy of aspirin and clopidogrel, on-treatment platelet reactivity was measured by VerifyNow P2Y12 testing at 12-24h after percutaneous coronary intervention (PCI). High platelet reactivity (HPR) and low platelet reactivity (LPR) were defined as P2Y12 reaction units (PRU) ≥280 and <190, respectively. Microarrays were used to perform miRNA expression profiling in purified platelets between 4 patients with HPR and 4 with LPR. The candidate miRNAs analyzed from microarrays were further validated by quantitative reverse-transcription polymerase chain reaction (RT-PCR) in platelets of 15 patients with HPR and 16 with LPR. The platelets of ACS patients were incubated with ABT-737 (a bcl-2 inhibitor, 2.5μM) in vitro for 2h at 37℃. The apoptotic events were measured by Annexin V-FITC/PI and JC-1 labeling. The megakaryocytic cell line MEG-01 was used for miRNA transfection experiments.
Results: 3 miRNAs (miR-145, -15b and -143) were detected to be differentially expressed in platelets between patients with HPR and LPR by microarrays. Among the candidate miRNAs, miR-15b was validated to downregulate in platelets of HPR patients compared with LPR patients by RT-PCR (P=0.017). MiR-15b was bioinformatically predicted to induce cell apoptosis via targeting bcl-2. In platelets, we confirmed that patients with HPR expressed higher levels of bcl-2 protein than those with LPR. The percentages of apoptotic platelets were significantly and inversely correlated with the PRU values in 37 ACS patients (P<0.001). Furthermore, ABT-737 was demonstrated to attenuate on-treatment platelet reactivity of ACS patients in vitro, consistent with decreased platelet apoptosis in patients with HPR. In cultured MEG-01 cells, the upregulation of miR-15b was concurrent with the downregulation of bcl-2 protein and enhanced megakaryocyte apoptosis. Besides, overexpression of miR-15b reduced the luciferase activity of a bcl-2 3'UTR reporter construct, indicating that bcl-2 is a direct target of miR-15b in megakaryocytes.
Conclusion: This study indentifies platelet miR-15b as a novel negative regulator of on-treatment platelet reactivity in patients with ACS and a pivotal role for platelet apoptosis in interindividual variability of platelet reactivity.

P6467 | BEDSIDE
Bleeding complications among myocardial infarction patients treated with clopidogrel, prasugrel or ticagrelor: preliminary results from nationwide danish registries

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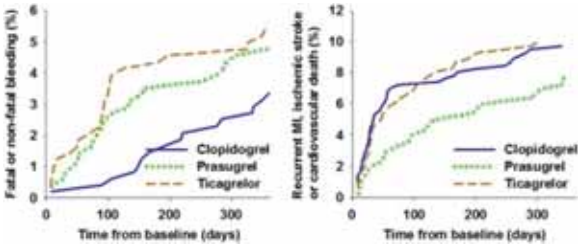
Purpose: We investigated the risk of bleeding among patients treated with Clopidogrel, Prasugrel or Ticagrelor in a nationwide cohort.
Methods: We included myocardial infarction (MI) patients >30 years admitted 2010-2011. Patients were followed 1 year. Treatment was identified from claimed prescriptions. Comorbidity and concomitant medication was identified by individual-level linkage of administrative registers. We matched equal numbers of patients treated with each drug on propensity-score in a subpopulation to avoid confounding. Hazard ratios (HRs) for 1) Fatal or non-fatal bleeding, requiring hospitalization and 2) Recurrent MI, ischemic stroke or cardiovascular death was assessed by Cox proportional Hazard Model adjusted for age, gender, comorbidity, concomitant medication, previous bleeding, alcoholism, PCI & CABG.
Results: A total of 9763 patients (mean age 69 SD 14, 64% male) were included. In the propensity-score matched subpopulation of 1455 patients, bleedings were more common among Ticagrelor and Prasugrel users compared to clopidogrel; 26 (5.4%) and 23 (4.7%) vs. 16 (3.3%), respectively. This was, however, not statistically significant in the Cox model; Ticagrelor HR: 1.71 (95%CI: 0.9-3.1, P=0.11) and Prasugrel HR: 1.71 (95%CI: 0.9-3.3, P=0.11), with clopidogrel as refererence. Prasugrel users had less adverse cardiovascular events than users of Ticagrelor and Clopidogrel; 37 (7.6%) vs. 48 (9.9%) and 47 (9.7%), respectively. This was however not statistically significant; Prasugrel HR: 0.71 (95%CI: 0.4-1.2, P=0.17).



Kaplan Meier analyses.

Conclusion: We found tendencies that Ticagrelor and Prasugrel increased the risk of bleeding compared to Clopidgrel, and that Prasugrel lowered the risk of adverse cardiovascular events. However, a larger population is needed to confirm these tendencies statistically.

P6468

ABSTRACT WITHDRAWN

P6469 | BEDSIDE
Long-term efficacy and safety of prasugrel compared to clopidogrel in patients with acute coronary syndromes in clinical practice. Results of the prospective German CPU registry

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Background: Prasugrel compared to clopidogrel has been associated with an improved outcome in patients with ACS undergoing PCI for acute coronary syndromes in the TRITON-TIMI 38 study. Little is known about the efficacy and safety of long-term treatment with prasugrel in daily clinical practice.
Methods: In the prospective German CPU registry patients with acute coronary

syndromes admitted to a chest pain unit and treated with either prasugrel or clopidogrel were enrolled. Baseline characteristics, antithrombotic therapies, interventional procedures features and events after 12 months were prospectively collected and centrally analysed. Here we compare the outcomes of 453 patients with prasugrel and a matched control group with clopidogrel.
Results: Baseline variables, procdural features and 12-months events are shown in the table.

12-month results

	Prasugrel (n=453)	Clopidogrel (n=453)
Age	59 yrs	61 yrs
Women	22%	23%
STEMI	46%	24%
PCI	92%	90%
Still on drug at 12 months	73%	76%
Death	2.2%	3.7%
Myocardial infarction	1.2%	2.9%
Stroke	1.7%	1.3%
MACCE	3,9%	7,3%
Bleeding	0,6%	1,0%

Conclusion: In this real life experience prasugrel compared to clopidogrel improved clinical outcome in patients with ACS without an increase in bleeding complications.

P6470 | BEDSIDE
Relationship between troponin levels and long-term outcomes in medically managed patients with non-ST-segment elevation acute coronary syndromes: insights from the TRILOGY ACS trial

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Purpose: The relationship between troponin (Tn) elevation and outcomes among patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS) is established, but is less well-studied in long-term follow-up of medically managed patients receiving contemporary antiplatelet therapy.
Methods: In 7038 medically managed NSTE ACS patients randomized in the TRILOGY ACS trial of prasugrel vs. clopidogrel and for whom peak Tn data were available, we examined relationships of categories of site laboratory-based peak Tn/upper limit of normal (ULN) ratio (<1×ULN [n=1849]; 1×-<3×ULN [n=1203]; 3×-<5×ULN [n=581]; and ≥5×ULN [n=3405]) within 48 h of the index ACS event (≈4.5 d before randomization) as an estimate of index infarct size with 30-month ischemic outcomes.
Results: Patients with Tn ratios <1×ULN were more likely to be younger, female, from Central/Eastern Europe, and have lower GRACE risk scores than patients with ratios ≥5×ULN. Conversely, patients with ratios ≥5×ULN were more frequently smokers but less often had prior myocardial infarction or percutaneous coronary intervention. Diabetes prevalence, body mass index, serum creatinine, and hemoglobin were similar across groups. Trends for increasing event rates across peak Tn categories were highly significant for all endpoints (Table). The relationship was stepwise for mortality but appeared to plateau for composite endpoints for Tn values >3×ULN. The most dramatic difference observed in event rates was between Tn <1×ULN and any Tn elevation ≥1×ULN during early follow-up.

Kaplan-Meier event rates at 30 months

	Troponin level				P_{trend}
Endpoint	<1×ULN	1×–<3×ULN	3×–<5×ULN	≥5×ULN	
CV death, MI, or stroke	12.2%	18.4%	26.6%	25.1%	<0.001
CV death or MI	11.5%	16.8%	25.0%	23.5%	<0.001
CV death	6.2%	9.6%	10.8%	12.8%	<0.001

Conclusions: Among NSTE ACS patients selected for medical management, there was a graded relationship of increasing peak Tn with long-term ischemic events. At 30 months, event rates for patients with Tn ≥5×ULN were more than twice the rates for patients with Tn <1×ULN.

P6471 | BEDSIDE
In-hospital bleeding in acute coronary syndrome patients undergoing percutaneous coronary intervention in the era of novel P2Y12 inhibitors: validation of the modified Mehran bleeding risk score

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Purpose: In-hospital bleeding events occur frequently in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) and may be affected by P2Y12 inhibitor used. We aimed to analyze in-hospital bleeding events in the context of a contemporary Greek Antiplatelet Registry (GRAPE).
Methods: In 2047 patients, predictive factors for in-hospital Bleeding Academic Research Consortium (BARC) type ≥2 events were analyzed. Bleeding rates were compared according to P2Y12 inhibitor used and modified Mehran bleeding score usefulness was assessed.
Results: Hospital BARC type ≥2 events occurred in 84 (4.1%). Novel P2Y12 inhibitor use, prior actionable bleeding, and hemodynamic instability at admission favored bleeding, whereas male gender was a protective factor (C-statistic 0.71, 0.66-0.77 95% CI, p<0.001). Following propensity matching, BARC type ≥2 bleeding rates were higher amongst novel P2Y12 inhibitor when compared with clopidogrel-treated patients (6.0% vs 2.7%, p=0.01), while did not differ between ticagrelor and prasugrel-treated patients (6.4% vs 3.6%, p=0.2). Modified Mehran risk score [median (1st-3rd quartile)] was higher in clopidogrel compared to novel P2Y12 inhibitor-treated patients [14 (9-19) vs 9 (6-14), p<0.001] and in ticagrelor compared to prasugrel-treated patients [10 (7-15) vs 9 (5-12), p<0.001], while exhibiting good calibration and adequate discriminative power.
Conclusions: In ACS patients undergoing PCI, novel P2Y12 inhibitors' use was associated, amongst other factors, with in-hospital BARC type ≥2 bleeding events. Novel P2Y12 inhibitors are accompanied by a higher rate of bleeding compared to clopidogrel, with no such difference observed between prasugrel and ticagrelor. Modified Mehran risk score might be efficiently applied for prediction of in-hospital severe bleeding events.

P6472 | BEDSIDE
Impact of atrial fibrillation on laboratory efficacy of P2Y12 receptor antagonists in patients after percutaneous coronary intervention

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Purpose: To verify whether the presence of atrial fibrillation (AF) impacts the platelet reactivity, particularly the efficacy of ADP receptor antagonists, and to verify whether there is a correlation between CHA2DS2VASc score and the efficacy of ADP receptor antagonists in the group of patients with AF after stent–PCI.
Methods: The analysis of PCI registry was performed. The efficacy of ADP receptor antagonists was measured by phosporylation of the VASP 24±4 hs after clopidogrel 600mg / prasugrel 60 mg / ticagrelor 180mg, and it was expressed through PRI–Platelet Reactivity Index. The high-on treatment platelet reactivity (HTPR) was defined by PRI ≥50%.
Results: The study group consisted of 760 patients (age 66.9±12.2 ys, 35.1% women). 114 of them had a history of AF (age 74.6±9.3 ys, 48.2% women) - chronic AF (50.8%) or paroxysmal AF (49.2%). The patients with AF were significantly older (74.6±9.3) than patients without AF (65.6±12.2, p<0.001). In the group of patients with AF, there were significantly more patients with cerebrovascular disease (p<0,001) and hypertension (p=0,006). 83% of patients were treated with clopidogrel, 17% with prasugrel or ticagrelor.
Laboratory efficacy of ADP receptor antagonists with respect to the presence of AF is shown in the Table. Within the clopidogrel group, HTPR was detected in 39.8% of patients with AF and 39.3% of patients without AF (n.s.) In the prasugrel/ticagrelor group, proportion of patients with HTPR was 18.18% in patients with AF and 8.6% in patients without AF (n.s.). The mean value of CHA 2DS2 VASc score in the group of patients with AF was 4.69±1.58. We did not find any correlation between CHA 2DS2 VASc score and efficacy of ADP receptor antagonists.
Conclusion: The presence of AF did not influence the efficacy of ADP receptor antagonists. CHA2DS2 VASc score did not predict the efficacy of ADP receptor antagonists nor the proportion of patients with HTPR.

Abstract P6472 – Table 1. Characteristic of PRI in dependence on AF and in dependence on AF and choice of antiplatelet drugs (clopidogrel vs. prasugrel/brilique)

	Patients with AF (n=114)			Patients without AF (n=646)			p (value)
	mean	median	IQR	mean	median	IQR	
Complete population study (n=760)	40,24±24,43	37,84	41,42	38,58±23,84	38,7	40,01	p=0,497
Patients treated with clopidogrel (n=633) (with AF, n=103; without AF, n=530	42,23±23,85	40,79	40,24	42,8±22,78	43,25	36,37	p=0,816
Patients treated with prasugrel/brilique n=127 (with AF n=11, without AF n=116)	21,62±22,76	12,11	15,06	19,23±18,16	12,36	16,34	p=0,684

P6473 | BEDSIDE

Effect of new p2y12 inhibitors in patients with chronic kidney disease after an acute coronary syndrome

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Background: Chronic Kidney Disease (CKD) concerns 35% of ACS patients and is associated with poor outcomes after stent implantation. New P2Y12 blocker (ticagrelor, prasugrel) has been largely unexplored in this specific population.
Methods: Consecutive patients admitted for Acute Coronary Syndrome and discharged on prasugrel or ticagrelor were screened and classified as: normal renal function (Glomerular filtration rate (GFR) >90 ml/ min), mild CKD (GFR 60 to 89 ml/min), moderate to severe CKD (GFR <60 ml/min). Platelet response was assessed at one month clinical follow-up by platelet reactivity index vasodilator-stimulated phosphoprotein (PRI-VASP)
Results: 515 patients were discharged from our institution with prasugrel 10 mg and 72 on ticagrelor 180mg. 293 patients (49%) were defined as normal renal function, 222 (38%) as mild CKD and 72 (12%) as moderate to severe CKD. We observed a significant correlation between PRI VASP and GFR for prasugrel and ticagrelor (r=0.30 p<0.0001 and r=0.26 p=0.03 respectively). On Prasugrel we observed significantly lower levels of PRI-VASP in CKD patients in comparison with normal renal function (24.4% ± 0.8 vs. 31.3% ± 0.8 p<0.0001). Conversely, in Ticagrelor treated patients no significant difference of PRI-VASP levels according to renal function status exists. (17.1% ± 1.8 vs. 22.4% ± 2.6 p=0.09 mild to sevre CKD versus normal renal function and 16.1% ± 2.7 vs. 19.1% ± 1.4 p=0.31 moderate to severe CKD versus mild CKD to normal renal function). On prasugrel bleeding is associated with lower GFR (85.8±2.8 vs. 94.3±1.4 p=0.01). In Ticagrelor cohort we do not observe any significant relation between GFR and bleeding events. (87.6±10.1 vs. 86.0±3.9 p=0.9)
Conclusion: New P2Y12 blockers are associated with more potent platelet inhibition in CKD patients. Platelet inhibition on ticagrelor is less dependent of renal function in comparison with prasugrel.

P6474 | BEDSIDE

Low complication rates of prasugrel therapy in interventionally treated STEMI-patients in clinical practice. 1-year follow-up data of the Bremer STEMI registry

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Purpose: In the randomized TRITON-TIMI 38 trial a reduction of ischemic events has been observed in STEMI-patients treated with prasugrel compared to clopidogrel, without a significant increase of bleeding complications.
Registry data to evaluate the efficacy and safety of prasugrel treatment in the "real-world" management of patients with STEMI are rare.
Methods: The Bremer STEMI registry (BSR) is a monocentric prospective registry of patients admitted to hospital due to STEMI. Data are collected in the Bremer heart center, which is exclusively responsible for 24-hours-PCI service in a large region in northwest Germany serving a population of about 800 000 residents.
In the present analysis 1-year follow-up data of patients treated with prasugrel compared to clopidogrel were investigated. To match the groups clopidogrel-patients with prasugrel-contraindications/warnings (prior stroke, age ≥75 years, <60 kilograms, triple therapy) were excluded.
Results: 712 interventionally treated STEMI-patients with prasugrel therapy and 1-year follow-up (time period 01/2010-07/2012) were compared to 1517 interventionally treated STEMI-patients with clopidogrel therapy (time period 01/2006-07/2012).
The baseline characteristics (age, gender, diabetes, coronary 3-vessel-disease, resuscitation) did not significantly differ between the groups.
1-year mortality and MACCE (death, nonfatal stroke, nonfatal reinfarction) were reduced in the prasugrel group, with a significant difference resp. MACCE (table).
Bleeding complications were not significantly different between the groups (prasugrel vs. clopidogrel in-hospital: 3.5% vs. 4.0% p=0.55; from discharge until 1 year: 0,7% vs. 0,9%, p=0.63).

	Prasugrel	Clopidogrel	p value
Mortality	4.1%	5.6%	0.126
MACCE (death, nonfatal stroke or reinfarction)	8.7%	11.9%	0.035

Conclusions: The data of the BSR show that prasugrel therapy in patients with STEMI is associated with low complication rates in clinical practice.
In comparison to matched clopidogrel-patients lower rates of MACCE were observed without significant differences in bleeding.

PERCUTANEOUS CORONARY INTERVENTION AND ANTIPLATELET THERAPY

P6476 | BEDSIDE

Procedural and clinical outcomes after glycoprotein IIb/IIIa inhibitor use for saphenous vein graft interventions

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Background: Percutaneous coronary intervention (PCI) of saphenous vein grafts (SVG) pose a high-risk for thrombo-embolic events. Glycoprotein IIb/IIIa inhibitors are frequently used, although the safety and efficacy of these drugs in this setting are unknown.
Methods: Patients with prior coronary artery bypass surgery were included who underwent PCI of ≥1 SVG graft at a Dutch academic center between January 1997 and December 2008. These patients were matched 1:1 based on the procedural use of abciximab using a propensity-score matching algorithm based on 17 variables. Conditional logistic regression and Cox regression stratified on matched pairs were performed to evaluate the association between abciximab use and the composite measure of mortality, myocardial infarction, stroke and repeat revascularization (MACCE) at 30 days and up to 1 year.
Results: The propensity-score matched cohort consisted of 236 patients, in whom complete 1-year follow-up was available in 98.3%. The composite of 30-day MACCE occurred in 18 patients (15.3%) in the abciximab group and 16 patients (13.6%) in the control group (odds ratio: 1.13 [0.57-2.21], p=0.73). At 1-year follow-up, MACCE rates were also similar (32.5% vs. 33.9%, hazard ratio: 0.97 [0.59-1.59], p=0.90). Bleeding (BARC type 3) was higher in the abciximab group (11.9% vs. 4.2%, OR: 2.80 [1.01-7.77], p=0.048). Subgroup analyses among patients based on clinical presentation and use of embolic protection devices, rendered similar results.
Conclusion: The use of intravenous abciximab did not result in improved clinical outcomes at 30 days as well as 1-year in patients undergoing SVG PCI, and is associated with increased bleeding.

P6477 | BEDSIDE

Impact of obesity and the metabolic syndrome on response to clopidogrel or prasugrel and bleeding isk in patients treated after coronary stenting

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Purpose: This study aimed to analyze the impact of body mass index (BMI) and the metabolic syndrome (MS) on responses to clopidogrel or prasugrel and bleeding risk after acute coronary syndrome (ACS).
Methods: 1542 consecutive patients undergoing coronary stenting were included (287 clopidogrel 75 mg, 868 clopidogrel 150 mg, and 387 prasugrel 10 mg). Platelet reactivity was assessed 1 month after discharge using PRI VASP.
Results: 336 (21.8%) patients were obese (BMI ≥30kg/m^2) and we observed higher platelet reactivity associated with higher BMI across thienopyridine regimens. Incidence of high on-treatment platelet reactivity (HTPR) (PRI VASP >50%) was higher in obese than non-obese patients (p<0.05 for all regimens). Conversely, incidence of low on-treatment platelet reactivity (LTPR) with prasugrel therapy (PRI VASP <20%) was lower in obese than non-obese patients: 13% (12/93) vs. 33% (97/294); OR [95%CI]: 0.30 [0.16-0.58]; p<0.001. Accordingly, incidence of BARC bleeding complications was higher in non-obese than in obese patients: 10% (119/1206) vs. 6% (20/336); OR [95%CI]: 1.7 [1.1-2.8]; p=0.03. This impaired response was only observed in obese patients with the MS while

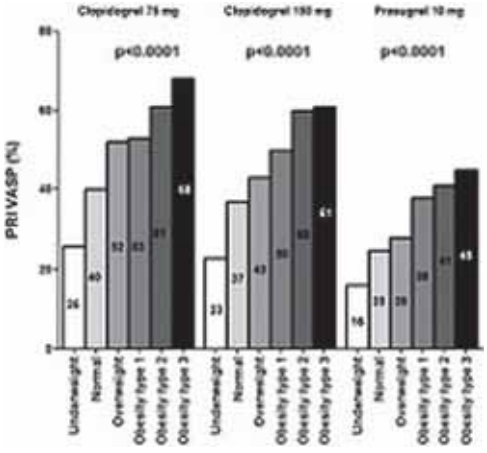

Figure 1

obese with the MS had significantly higher platelet reactivity than other obese patients with all regimens ($p<0.01$). Obese without the MS had no significant difference of platelet reactivity compared with non obese patients.
Conclusion: The present study confirmed that BMI has a strong impact on response to clopidogrel and prasugrel with higher HTPR incidence, lower LTPR incidence and lower bleeding complication in obese patients. The presence of the MS strongly affects response to antiplatelet agents, indicating that the metabolic status might be a better predictor of platelet inhibition than BMI.

P6478 | BEDSIDE
Incremental usefulness of genetic testing of clopidogrel therapy over conventional clinical risk factors for prediction of major cardiovascular events after drug-eluting stent implantation

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Purpose: To determine a incremental prognostic value of combined status of ABCB1 3435C->T and CYP2C19 variant allele on major adverse cardiac and cerebrovascular events (MACCE) over clinical risk factors using C-statistic and novel risk reclassification metrics (NRI: net reclassification index, IDI: integrated discrimination improvement) in a real-world PCI cohort taking clopidogrel.
Method: We consecutively enrolled 2188 patients undergoing PCI. For CYP2C19 genotype, patients were classified into 3 groups: extensive (EM, *1/*1,*/*17), intermediate (IM, *1/*2,*1/*3), poor (PM, *2/*2,*2/*3,*3/*3) metabolizer. For ABCB1 3435C>T, patients were stratified into CC,CT,TT. To assess combined effect of both genetic variants, patients were stratified into 4 groups according to the presence of CYP2C19 PM and ABCB1 TT: non-CYP2C19 PM + non-ABCB1 TT, non-CYP2C19 PM + ABCB1 TT, CYP2C19 PM + non-ABCB1 TT, CYP2C19 PM + ABCB1 TT. The primary endpoint was the composite of 1-year MACCE including any death,nonfatal MI or stroke.
Results: On multivariate Cox analysis, when combined 4 genetic categories were incorporated into the clinical model, patients with both CYP2C19 PM and ABCB1 TT had 5-fold higher hazard of MACCE (HR: 5.06; 95%CI: 2.12 to 12.09; $p<0.001$) than carriers of neither. However, the addition of genetic variant neither yield further improvement in predictive performance in model (C-statistic: clinical model, 0.782; clinical + genetic model, 0.788; difference, 0.006; p=0.66) nor reclassification of individual at risk (model IDI, 0.002 [95% CI: -0.001 to 0.04; p=0.06], relative IDI, 0.269 [95%CI: 0.26 to 0.27; p=0.17], continuous NRI, 0.126 [95% CI: 0.001-0.25; p=0.28],NRI categories, 0.039 [95%CI: -0.02 to 0.09; p=0.20]).

Table 1. C-statistic of each model

Model	C-statistic	95% CI	Estimated difference (95% CI)	p-value
Clinical model*	0.782	0.76–0.80	Reference	Reference
Clinical model* + CYP2C19 phenotype	0.787	0.77–0.81	0.005 (–0.011–0.022)	0.54
Clinical model* + ABCB1 3435 C>T genotype	0.783	0.76–0.80	0.001 (–0.019–0.021)	0.93
Clinical model* + Genetic model	0.788	0.77–0.80	0.006 (–0.012–0.024)	0.51

*Including age, BMI, HBP, diagnosis, CRF, prior stroke, LVEF <40%, left main disease.

Conclusions: Although the combined status of CYP2C19 and ABCB1 3435 C>T variant alleles was strong independent predictor for 1-year MACCE, it was not a useful marker for prediction of MACCE over conventional clinical risk factors in a real-world PCI cohort taking clopidogrel

P6479 | BEDSIDE
Lower on-treatment platelet reactivity at the time of stent placement contributes to the resolution of post-procedural intra-stent thrombus: serial OCT observation in PRASFIT-elective

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Purpose: We examined the impact of on-treatment platelet reactivity at the time of elective percutaneous coronary intervention (PCI) on resolution of intra-stent thrombus (IS-Th) observed immediately after stent implantation.
Methods: PRASFIT-Elective is a multicenter, parallel-group study of PCI patients receiving either prasugrel (20/3.75 mg, loading/maintenance dose) or clopidogrel (300/75 mg), in addition to aspirin (100mg). Among a total of 111 patients who were predefined for inclusion in the optical coherence tomography (OCT) substudy, 82 patients underwent immediately after stenting and 8-month follow-up. Serial OCT divided them into two groups according to the time course of IS-Th; resolved IS-Th group or persistent IS-Th group. Resolved IS-Th was defined as the protruding irregular luminal masses over 100μm in maximal length with dorsal shadowing after stenting on post-procedural OCT, but not observed on 8-month follow-up OCT, while persistent IS-Th as that observed on both post-procedural and 8-month follow-up OCT. On-treatment platelet reactivity, P2Y12 Reactive Unit (PRU), was determined by the VerifyNow® P2Y12 assay at index PCI, 4 and 48 weeks after PCI.
Results: Among 132 IS-Th detected immediately after stenting, 22 cases were classified into persistent IS-Th group by 8-month follow-up OCT. Cases with resolved IS-Th showed lower PRU compared to cases with persistent IS-Th (231.7±92.4 vs 282.0±113.6, p=0.027, respectively) at PCI, while there were no significant differences in PRU at 4 weeks and 48 weeks after PCI. Results of univariate logistic regression analyses for the resolution of IS-Th revealed that lower PRU at PCI, absence of calcified lesions, and de novo lesions were identified (Table).

Table 1. Univariate logistic regression analysis for the factors indicating to resolve intra-stent thrombus

Variables	Odds ratio	95% CI	P value
P2Y12 Reactive Unit at stenting	0.994	0.989 to 0.999	0.030
Calcified lesion	0.227	0.075 to 0.682	0.008
De novo lesion	3.438	1.021 to 11.575	0.046

Conclusions: Besides local lesion-related factors, lower on-treatment platelet reactivity through P2Y12 inhibition at the time of PCI contribute to regression of IS-Th formed immediately after PCI, which might contribute to better vessel healings following stent placement.

P6480 | BEDSIDE
On-clopidogrel platelet reactivity as predictor for long-term clinical outcome in patients after planned discontinuation of clopidogrel

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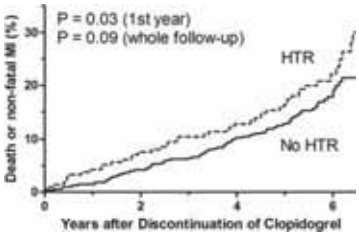
Background: High on-treatment platelet reactivity (HPR) has been clearly linked to worse clinical outcome in patients on clopidogrel and after coronary stent implantation (PCI). It is unknown whether this effect persists after planned discontinuation of clopidogrel.
Methods: This analysis included 765 consecutive patients undergoing elective PCI after loading with clopidogrel 600mg. Clopidogrel was continued for 6 months after implantation of drug-eluting stents and for 1 month if only bare-metal stents were used. Platelet reactivity was tested by optical aggregometry (5 μM ADP) on day 1 after coronary stenting and after intake of first maintenance dose of clopidogrel 75mg. HPR was defined as >14% residual aggregation. Patients were followed for up to 7 years. The combined primary endpoint was death of any cause or non-fatal myocardial infarction (MACE).
Results: At time of enrollment, HPR was found in 217 of 765 patients (28%). During a median follow-up of 5.7 years, MACE occurred in 145 subjects after planned discontinuation of clopidogrel. Patients with HPR showed a higher incidence of MACE after discontinuation of clopidogrel (Figure; unadjusted HR: 1.34, 95%-CI 0.95-1.89, p=0.09). However, landmark analyses demonstrated that this association was only significant within the first year after discontinuation (unadjusted HR: 2.93, 95%-CI 1.13-7.60, p=0.03; adjusted HR: 3.09, 95%-CI 1.11-8.60, p=0.03), but not in the time stratum beyond 1 year after discontinuation (unadjusted HR: 1.19, 95%-CI 0.82-1.72, p=0.37).



Conclusions: Patients with HPR persist to be at high risk for MACE even after the end of the planned treatment period with clopidogrel. However, this association is only valid for the first year after end of treatment.

P6481 | BENCH
The impact of triple anti-platelet therapy for endothelialization and inflammatory response at overlapping bioabsorbable polymer coated drug-eluting stents in a porcine coronary model

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Background: This study was conducted to evaluate the endothelialization and the inflammatory responses depending on the administration duration of triple anti-platelet therapy at overlapping bioabsorbable polymer coated biolimus-eluting stents (BESs) in a porcine coronary model.
Methods: We successfully deployed 36 overlapping BESs for the left anterior descending coronary and left circumflex artery or right coronary artery in 18 non-injured pigs. Total pigs were divided into 3 groups (12 overlapping stents of 6

pigs in each group) as follows: group I received aspirin 100mg and clopidogrel 75mg daily for 8 weeks, group II received aspirin 100mg and clopidogrel 75mg daily for 8 weeks and cilostazol 200mg daily for initial 4 weeks, group III received aspirin 100mg, clopidogrel 75mg, and cilostazol 200mg daily for 8 weeks. Follow-up coronary angiograms and histomorphometric and histopahtologic analyses at overlapping and non-overlapping segments were performed respectively.
Results: Inflammation score was similar between overlapping and non-overlapping segments in all pigs (1.2±0.33 vs. 1.1±0.17, p=0.117). The neointima area (NA) and percent area stenosis (%AS) at overlapping segments were not significantly different among 3 groups. However, at non-overlapping segments, NA and %AS in group III were significantly smaller than those in group I (2.3±0.50 mm^2 vs. 1.8±0.43 mm^2, p=0.037; 48.9±12.85% vs. 37.7±9.08%, p=0.031).
Conclusions: Our study shows that BES appears to be reliable on the inflammatory response at overlapping segments as well as non-overlapping segments. Long-term administration of cilostazol is more effective in reducing neointimal formation at non-overlapping segments of BESs in a porcine coronary model.

P6482 | BEDSIDE
Impact of smoking after percutaneous coronary intervention in patients treated with clopidogrel: real-world findings from the PARIS registry

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Purpose: Results from clinical trial participants undergoing PCI with stents suggest that the clinical benefits of clopidogrel in reducing thrombotic events are accentuated in smokers versus non-smokers. Whether these associations persist in unselected real-world patients after PCI remain unknown. Results from clinical trial participants undergoing PCI with stents suggest that the clinical benefits of clopidogrel in reducing thrombotic events are accentuated in smokers versus non-smokers. Whether these associations persist in unselected real-world patients after PCI remain unknown.
Methods: The PARIS registry was a multicenter prospective observational study of 5,018 patients undergoing PCI with stents. Smoking status was classified as current or not-current (quit over 1 month or never smoked). Dual antiplatelet therapy (DAPT) cessation was categorized as physician-guided discontinuation, brief interruption or disruption due to non-adherence or bleeding. Adverse events and DAPT cessation were compared between groups using Cox regression.
Results: Smokers (n=902, 19%) were younger and more often male with lower prevalence of diabetes mellitus, hypertension or prior CAD compared to non-smokers (n=3733, 81%). Over 2 years smokers were less likely to interrupt DAPT (8.3% vs. 10.9%, p=0.02), while disruption was more common in smokers (17.1% vs. 13.6%, p=0.01). Discontinuation did not differ between groups. Ischemic adverse events were significantly higher among smokers vs. non-smokers and persisted after multivariable adjustment.

Hazard ratios for adverse event

	Crude Risk		Adjusted Risk	
	HR [95% CI]	p Value	HR [95% CI]	p Value
Major Adverse Cardiac Events	1.43 [1.10, 1.86]	0.0081	1.86 [1.38, 2.49]	< 0.0001
Cardiac Death	1.35 [0.92, 1.98]	0.1290	2.32 [1.51, 3.57]	0.0001
Myocardial Infarction	1.48 [1.04–2.09]	0.0274	1.59 [1.08, 2.35]	0.0188
Probable/Definite Stent Thrombosis	2.16 [1.29–3.61]	0.0033	1.86 [1.03, 3.35]	0.0402

HR=Hazard Ratio; CI=Confidence Interval.

Conclusions: In contrast to findings from clinical trial populations, among unselected patients smoking is associated with higher rates of disruption and adverse events compared to non-smokers.

P6483 | BEDSIDE
Validation of a therapeutic window for P2Y12-inhibition: collaborative analysis of the relation between platelet reactivity, stent thrombosis and bleeding

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Purpose: Studies have shown that platelet reactivity during treatment with P2Y12-inhibitors may predict the risk of stent thrombosis (ST) and major bleeding. However, validation of standardized cutoffs of platelet reactivity is lacking. We aimed to evaluate a therapeutic window concept for the prognostic impact of platelet reactivity, categorized as low (LPR), normal (NPR) or high (HPR) in the Western population of patients undergoing PCI during treatment with clopidogrel or prasugrel.
Methods: Using standardized platelet reactivity cutoffs, we performed a collaborative post-hoc analysis from previously published studies reporting the association between major bleeding, ST and platelet reactivity after PCI. LPR-NPR-HPR categories were defined as <95, 95-208 and >208 PRU for VerifyNow, <19, 19-46, and >46 U for Multiplate and <16, 16-50 and >50% for VASP assays, respectively. Definite or probable ST, major bleeding (study defined) and all-cause mortality were evaluated at the longest follow-up available.
Results: A total of 17 studies including 18,772 patients qualified for the analysis. Patients with HPR had a 2.7-fold higher risk for ST (p<0.0001) but a 17% lower risk for bleeding (p=0.03) compared to those with NPR. In turn, patients with LPR had a 1.8-fold higher risk for major bleeding (p<0.0001) but similar risk for ST (p=0.96) as those with NPR. The risk of all-cause mortality was significantly higher in HPR patients compared to others (p=0.0003). There was no interaction between different platelet function assays in predicting the higher risk for ST or bleeding (pint>0.15).
Conclusions: Patients on P2Y12-inhibitors undergoing PCI exhibiting HPR or LPR have an increased risk for ST and bleeding, respectively. The lowest rates of adverse events in NPR patients suggest the presence of a therapeutic window for platelet reactivity. Further randomized studies are warranted to test the safety and efficacy of reaching such therapeutic target following PCI.

P6484 | BEDSIDE
VERifynow in Dlabetes high-on-treatment platelet reactivity: a pharmacodynamic study on switching from clopidogrel to prasugrel (VERDI study)

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Purpose: Diabetic patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) frequently exhibit high platelet reactivity (HPR) while on clopidogrel. We aimed to test the hypothesis that in diabetic patients with ACS undergoing PCI exhibiting HPR after standard treatment with clopidogrel, a loading dose of 60 mg of prasugrel followed by at least one 10 mg manteinance dose is superior to the standard treatment with clopidogrel for the achievement of optimal P2Y12 inhibition within the first 24-36 hours post-PCI.
Methods: The VERDI was a prospective, randomized, single-center, single-blind, parallel design study (NCT01684813). Consecutive diabetic patients with ACS undergoing PCI and loaded with clopidogrel were considered for platelet reactivity (PR) assessment immediately before PCI with the VerifyNow assay (Accumetrics Inc, San Diego, CA), measured in P2Y12 reaction units (PRU). Out of 63 screened patients, 50 (79.3%) patients were found with HPR (defined as PRU ≥208) and were randomized to receive a loading dose of 60 mg prasugrel vs the standard dose of clopidogrel. Platelet function was assessed again 24h post-PCI.
Results: Greater platelet inhibition was achieved by prasugrel compared with clopidogrel at 24h post-PCI (PRU 54±53.8 vs 284±69.3, respectively; p<0.001). The primary end point of non-HPR rate (PRU <208) at 24h post-PCI was higher in the prasugrel group, twenty-five patients (100%) in the prasugrel group achieved optimal antiaggregation versus 4 patients (16%) in the clopidogrel group; p<0.001. No significant acute bleeding was documented in either group.
Conclusion: Among type 2 diabetic patients with ACS and HPR undergoing PCI with stent, switching from clopidogrel to prasugrel was superior to standard treatment with clopidogrel for the achievement of optimal antiaggregation within the first 24h post-PCI.

P6485 | BEDSIDE
Clopidogrel tailored therapy in elderly patients undergoing percutaneous coronary intervention for acute coronary syndrome: the responsiveness to clopidogrel and stent thrombosis 2- ACS (RECLOSE 2-ACS

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Purpose: Clopidogrel is still the most used P2Y12 inhibitor in acute coronary syndrome (ACS) patients ≥75 years, and prasugrel therapy is relatively contraindicated in these subjects. High residual platelet reactivity (HRPR) on clopidogrel has been associated with high risk of ischemic events after percutaneous coronary intervention (PCI). Old age is a strong predictor of both HRPR on clopidogrel and bleeding events. The aim of this study was to evaluate the clinical outcomes after clopidogrel tailored antiplatelet therapy in ACS elderly (≥75 years) patients.
Methods: Residual platelet reactivity was assessed 12 to 24 h after clopidogrel 600 mg loading dose by light transmittance aggregometry (LTA) in 1789 consecutive ACS patients undergoing PCI. Patients with HRPR (≥70%) received a tailored therapy, generally based on an increased clopidogrel maintenance dose (150-300 mg/d). The primary end point was the composite of cardiac death, myocardial infarction, any urgent coronary revascularization, and stroke at 2-year follow-up.
Results: Among enrolled patients, 665 (37%) had ≥75 years. HRPR rate was 19% vs 11% in the elderly and non elderly group, respectively (p<0.0001). After tailored antiplatelet therapy in patients with HRPR, LTA test result was not

different in the 2 study groups (62±15% and 65±14% in the elderly and non elderly, p=0.219). At 2-year follow-up, primary end-point rate was 14% vs 11% (p<0.0001), cardiac death rate was 8% vs 3% (p<0.0001) and stent thrombosis rate 4.4% vs 2.7% (p=0.049) in elderly vs non elderly patients, respectively. In elderly patients, cardiac death rates was 13% vs 7% (p=0.017) in patients with and without HRPR.
Conclusions: Among ACS patients treated with clopidogrel after PCI, elderly patients were more likely to experience HRPR on clopidogrel than younger patients. Moreover, HRPR status in elderly patients is significantly associated with increased risk of ischemic events, cardiac death and stent thrombosis even after increased clopidogrel dose according to the results of platelet function tests.

P6486 | BEDSIDE
Use of clopidogrel, aspirin and oral anti-coagulant therapy in patients undergoing percutaneous coronary intervention: a meta-analysis of randomized controlled trials and adjusted observational result

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Introduction: The optimal antiaggregant therapy after coronary stenting in patients under oral anticoagulation (OAC) is currently debated.
Methods: Medline and Cochrane Library were searched for studies reporting outcomes of patients undergoing PCI and who were on triple therapy (TT) or double therapy (DT either aspirin and clopidogrel or OAC and clopidogrel). Major bleeding was the primary end point, while all-cause death, myocardial infarction (MI), stent thrombosis and stroke were secondary ones. Results were reported for all studies, and separately for those deriving from randomized controlled trials or multivariate analysis.
Results: In eight studies 1354 patients treated with double therapy (DT) were on aspirin and clopidogrel: a significant reduction of major bleeding for DT patients was demonstrated for overall studies and for the subset of RCT and observational studies providing adjusted data (odds ratio OR 0.46 [95% confidence interval 0.36-0.65] and OR 0.36 [0.28-0.46]). No increase risk of major adverse cardiac events (MACE: death, myocardial infarction, stroke and stent thrombosis) was reported (OR 0.85 [0.57-1.28]), although not deriving from randomized controlled trials or multivariate analysis.
Six studies with 5758 patients tested OAC and clopidogrel as DT with a significant reduction of bleeding (0.79 [0.63, 0.98]), without affecting rates of death, myocardial infarction, stroke and stent thrombosis (0.90 [0.69, 1.17] I2) also when including clinical data from randomized controlled trials or multivariate analysis.
Conclusions: When compared to TT, DT (clopidogrel and OAC or aspirin and clopidogrel) reduces bleeding. No difference in major adverse cardiac events is present for DT with OAC and clopidogrel, while only low grade evidence is present for aspirin and clopidogrel.

P6487 | BEDSIDE
Comparison of laboratory efficacy of P2Y12 receptor antagonists and predictors of high on-treatment platelet reactivity

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Objective: To compare the laboratory efficacy of P2Y12 receptor antagonists and to identify predictors of high on-treatment platelet reactivity (HTPR) in patients with an acute coronary syndrome treated with stent-PCI.
Methods: An analysis of PCI-VASP "all-comer" registry was performed. Efficacy of P2Y12 receptor antagonists was measured by phosphorylation of VASP 24±4 hours after a loading dose (LD) of clopidogrel (600mg), prasugrel (60mg) and ticagrelor (180mg), and expressed through a platelet reactivity index (PRI). High on-treatment platelet reactivity (HTPR) was defined as PRI ≥50%.
Results: Study group consisted of 589 patients who received clopidogrel (N=407, age 67±12.9 ys, 63.6% males), prasugrel (N=106, age 61.8±11.7 ys, 71.4% males) or ticagrelor (N=76, age 65.8±13.3 ys, 67.1% males). Patients selected for therapy with prasugrel were significantly younger than those who received clopidogrel (p=0.001).
Mean PRI was 44.2±23.1% after clopidogrel, 17.7±18.0% after prasugrel, and 18.8±17.0% after ticagrelor; p<0.001 for comparison of clopidogrel vs. prasugrel, and clopidogrel vs. ticagrelor, resp.). Proportion of patients with HTPR was 42.2% in clopidogrel group, 9.4% in prasugrel group, and 7.9% in ticagrelor group; p<0.001 for comparison of clopidogrel vs. prasugrel, and clopidogrel vs. ticagrelor, resp.).
From multiple variables* tested in prediction of HTPR, we found that HTPR was in ticagrelor treated patients significantly related to the platelet count (p=0.014), mean platelet volume (p=0.029) and multivessel disease (p=0.023). HTPR in patients treated with prasugrel was significatly related only to the mean platelet volume (p=0.02).
*variables included in the model: age, gender, BMI; history of: hypertension, diabetes, hyperlipidemia, MI, CABG, PAD, stroke, family history of CAD, cigarette smoking, CKD; therapy with: statin, ACEI, betablocker; single vs. multivessel disease, number of implanted stents; serum urea, creatinin, estimated GFR, hemoglobin, platelet count, mean platelet volume.
Conclusion: Residual platelet reactivity and proportion of patients with HTPR after LD of prasugrel/ticagrelor were significantly lower than after LD of clopidogrel. Factors known as predictors of higher platet reactivity did not influence efficacy of new generation of P2Y12 receptor antagonists. Family history of coronary artery disease platelet count and mean platelet volume were the single variables significantly related to HTPR in patients treated with prasugrel/ticagrelor.

PLATELETS AND ANTIPLATELET THERAPY: MISCELLANEOUS

P6489 | BEDSIDE
Thrombopoietin and platelet aggregation in patients with stable coronary artery disease

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Purpose: Thrombopoietin (TPO) has been suggested to possess a priming effect on platelets thereby potentiating platelet activation in response to different agonists. Furthermore, TPO has been shown to stimulate platelet-leukocyte interactions in whole blood through expression of P-selectin. The aim of the study was to investigate the association between platelet aggregation, TPO and platelet activation in stable coronary artery disease (CAD) patients treated with aspirin. Furthermore, we aimed at exploring the distribution of TPO levels in CAD patients with different clinical characteristics.
Methods: We studied 900 stable CAD patients with a relatively high-risk profile since 795 (88%) had a history of prior myocardial infarction, 250 (28%) had type 2 diabetes and 170 (19%) had both. All patients received 75 mg aspirin daily as mono antiplatelet therapy. Platelet aggregation was assessed by the VerifyNow Aspirin Assay and by multiple electrode aggregometry (MEA, Multiplate Analyzer) with arachidonic acid (AA) 1.0 mM and collagen 1.0 μg/mL used as agonists. TPO was assessed by ELISA. Platelet activation was evaluated by soluble P-selectin (sP-selectin), and cyclooxygenase-1 inhibition was assessed by measurement of serum thromboxane B2 using ELISA.
Results: TPO and platelet aggregation levels were significantly, though weakly, associated according to the VerifyNow Assay (r=0.07, p=0.03) and AA-induced MEA platelet aggregation (r=-0.09, p=0.01), whereas no association was found with collagen-induced MEA platelet aggregation (r=-0.03, p=0.43). TPO and sP-selectin did not correlate (r=-0.01, p=0.70). Smokers had significantly higher levels of TPO and sP-selectin than non-smokers (p-values≤0.02), and patients aged <65 years had significantly higher TPO levels than patients ≥65 years (p=0.02). In a multivariate linear regression analysis, TPO (p=0.01) and sP-selectin (p<0.0001) were independent predictors of AA-induced MEA platelet aggregation after adjustment for age, gender, smoking, body mass index and diabetes. Compliance with aspirin was confirmed by low serum thromboxane B2 levels in all patients (median ng/mL [25%;75%]: 0.97 [0.52;1.97]).
Conclusion: In stable, high-risk CAD patients, TPO and platelet aggregation were weakly associated. However, when adjusting for clinical characteristics, TPO was an independent determinant of platelet aggregation. Our results suggest that the priming effect of TPO on platelets is influenced by several factors, and that the priming effect is only modest in stable CAD patients treated with aspirin.

P6490 | BEDSIDE
Pharmacokinetic and pharmacodynamic effects of ticagrelor and dabigatran etexilate coadministration in healthy male volunteers

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Purpose: Ticagrelor is an antiplatelet agent and P-gp inhibitor and may thus have the potential to increase dabigatran plasma concentration on coadministration.
Methods: This open-label, fixed sequence, multiple-dose trial assessed the pharmacokinetic (PK) and pharmacodynamic (PD) effects of ticagrelor and dabigatran etexilate (DE) coadministration under steady-state conditions in 48 healthy Caucasian male volunteers. In part 1 (n=24), a single loading dose of ticagrelor 180 mg (T180), followed by multiple dosing of 90 mg bid (T90, maintenance dose) were given concomitantly with DE 110 mg bid (DE110); in part 2 (n=24), T180 was given 2 h after DE110 had been dosed to steady state.
Results: Dabigatran exposure increased ~1.3 fold under steady-state conditions when DE110 was coadministered with T90 maintenance dose (geometric mean

test/reference [T/R] ratios for area under the steady-state plasma concentration-time curve over a uniform dosing interval τ at steady state [AUCτ,ss]: 126% (90% confidence interval [CI] 107–149%). Dabigatran exposure was ∼1.5-fold higher after T180 coadministration (AUCτ,ss T/R ratio: 149% (90% CI 124-179%); and was ∼1.3 fold higher when T180 was given 2 h after DE110: AUCτ,ss T/R ratio: 127% [90% CI 108-149%]). The dabigatran concentration vs. diluted thrombin time relationship was linear, and the dabigatran concentration vs. activated partial thromboplastin time relationship was nonlinear. The PK/PD relationship of DE110 was unaltered when administered with T180 (either coadministered or given 2 h after) or with maintenance dose of T90.
Conclusion: There was only a mild increase in dabigatran steady-state exposure under ticagrelor maintenance therapy and when ticagrelor therapy was initiated with a staggered administration of ticagrelor. As with any antiplatelets plus anticoagulants combination, a pharmacodynamic enhancement based on the mode of action of these two drug classes needs to be considered, and an individual benefit-risk assessment is recommended. The combination of ticagrelor (T180 loading dose or T90 maintenance dose) and DE110 was well tolerated in healthy male volunteers.

P6491 | BENCH
Phosphorothioate oligonucleotides are potent platelet activators

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Purpose: Platelets mediate haemostasis and inflammatory processes and are crucial for immune responses. They express several toll-like receptors (TLRs) which are essential to early processes of immune reactions. The discovery of immunostimulatory properties of TLR9 stimulating short single-stranded, methylated DNA oligonucleotides (ODNs) provides new options for prophylaxis and/or therapy for infectious, allergic and malignant diseases. To prevent them from being rapidly degraded by nucleases, phosphorothioate (PS) modification was utilised whereby non-bridging oxygen molecules were replaced with sulfur. We were investigating the possible impact of synthetic TLR9 agonists on platelet activation.
Methods: Human platelets were incubated with ODNs in different modifications and concentrations (0.5-5μM). In vitro platelet activation was evaluated by flow cytometry and light transmittance aggregometry. The impact of TLR9 on ODN-induced platelet activation was determined by ODN pre-incubation of wild-type (WT) and TLR9−/− mouse platelets. Platelet adhesion to collagen (100μg/mL) and fibrinogen (100μg/mL) under flow conditions was assessed using a microfluidics system. In vivo experiments were performed by intravenous injection (0.6-1.0mg/kg body weight) of ODNs in C57BL6 mice, which were subsequently subjected to ferric chloride-induced carotid artery injury or examined for the occurrence of pulmonary embolism, respectively.
Results: Whilst investigating the possible impact of synthetic TLR9 agonists on platelets, we observed strong concentration-dependent platelet activation, as determined by P-selectin expression in flow cytometry and platelet aggregation. Unexpectedly, platelet activation was sequence- and TLR9-independent, but required PS backbone modifications of ODNs. ODNs with a native phosphodiester backbone (ODN non-mod) did not bind to or activate platelets. Moreover, PS ODN induced extensive thrombus formation was observed under flow conditions. In the carotid artery injury mouse model, significantly reduced occlusion times after ODN injection were observed, while intravenous administration of ODN non-mod did not alter time to vessel occlusion. Also, pulmonary thrombus formation could be detected compared to PBS control or non-modified ODN. Both mouse models confirm the relevance of platelet-activating effects of PS ODN in vivo.
Conclusion: Our data demonstrate a novel, unexpected, PS backbone-dependent, platelet-activating effect of oligonucleotides. As PS modification is a common step in many drug development programs this unforeseen effect should be considered.

P6492 | BENCH
Impact of genetic variation in the 5-HT transporter and receptor on platelet function in patients with stable CAD taking aspirin

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Background: Serotonin (5-HT) induces platelet aggregation by activating its 5-HT2A receptor. Platelet uptake is mediated by the 5-HT transporter (5-HTT). A common 5-HTT promoter (5-HTTLPR) splice variant results in long (L) and short (S) alleles. 5-HTTLPR genotype has been associated with increased platelet activation and risk of MI. Variation within HTR2A gene (C1354T) that encodes the 5-HT2A receptor has also been associated with enhanced platelet aggregation. We hypothesised that 5-HTT and/or HTR2A variation may influence platelet response to aspirin in patients with stable CAD.
Methods: Patients (n=144) with stable cardiovascular disease taking aspirin were genotyped for the 5-HTTLPR and HTR2A variants. Platelet inhibition was assessed by serum thromboxane and arachidonic acid-induced platelet aggregation assay.
Results: 5-HTT genotype (LL vs *S) was a significant determinant of serum TX level (8.9±2.6 vs 6.0±1.6 respectively; $p<0.02$) and 5-HTT LL genotype predicted an incomplete aspirin response (serum TXB2 >2.2ng/ml) (p=0.04; OR=2.22, CI=1.03-4.79). Odds ratio for the effect of LL genotype on TX elevation was 3.8 (95% CI 1.2-11.6) in younger patients (<64yrs) compared to 1.0 (95% CI=0.3-3.8) in older subjects. LL genotype did not influence AA aggregation (p=0.83, OR=1.2, CI=0.3-4.1). The HTR2A variant had no effect on TX generation (p=0.70; OR=1.22, CI=0.45-3.26) nor AA aggregation (p=0.99; OR=1.0, CI=0.2-4.9).
Conclusions: In younger patients with stable CAD 5HTT LL genotype carried by almost one third of our cohort is associated with a diminished response to aspirin that may increase cardiovascular risk. Genotypic variation in platelet activation appears to be a contributing mechanism.

P6493 | BEDSIDE
Platelet reactivity is associated with arterial stiffness in patients after percutaneous coronary intervention treated with dual antiplatelet therapy

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Purpose: Individual platelet response to antiplatelet therapy depends on genetic, cellular and clinical factors. We evaluated the effect of vascular function on platelet activation in patients after percutaneous coronary intervention (PCI) treated with dual antiplatelet therapy.
Methods: We consecutively enrolled 408 patients with stable coronary artery disease one month after successful PCI. All subjects were receiving dual antiplatelet therapy with aspirin (100mg/day) and clopidogrel (75mg/day) for at least one month at the time we evaluated their platelet reactivity and arterial function. Carotid-femoral pulse wave velocity (PWV) was measured as an index of aortic stiffness and augmentation index (AIx) as an index of arterial wave reflections. High on treatment platelet reactivity was evaluated using VerifyNow Assay. VerifyNow reports its results in P2Y12 reaction units (PRU) and the diagnostic cut-off value is 230 PRU.
Results: Importantly, subjects with high on treatment platelet reactivity and PRU>230 had significantly increased PWV (8.81±2.25 m/sec vs. 7.69±1.95 m/sec, p=0.001) and AIx (25.27±8.67% vs. 20.87±10.57%, p=0.04) compared to subjects with PRU≤230.
Conclusions: We documented an association between a direct measurement of platelet activation and vascular function in patients after PCI treated with dual antiplatelet therapy. As platelet reactivity is associated with long-term cardiovascular events after PCI the introduction of another clinical factor implicated in the variability of individual platelet response to antiplatelet therapy is of great importance.

P6494 | BEDSIDE
Effects of clopidogrel, prasugrel and ticagrelor on endothelial function and platelet reactivity in patients after percutaneous coronary intervention

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Purpose: The clinical benefit of clopidogrel, prasugrel and ticagrelor has been attributed to their antiplatelet effects. Endothelial function and arterial stiffness has an independent predictive value for cardiovascular events. We studied the different impact of clopidogrel, prasugrel and ticagrelor on endothelial function and platelet reactivity in coronary artery disease (CAD) patients.
Methods: We consecutively enrolled 45 patients with stable CAD one month after percutaneus coronary intervention (PCI): 15 patients receiving prasugrel regimen (10mg/d), 15 patients receiving clopidogrel regimen (75mg/d) and 15 patients receiving ticagrelor regiment (180mg/d). Angiography categorized subjects in with those single-vessel (1VD) or multivessel (2VD, or 3VD) CAD. Endothelial function was evaluated by flow mediated dilation (FMD) in the brachial artery. High on treatment platelet reactivity was evaluated using VerifyNow Assay. VerifyNow reports its results in P2Y12 reaction units (PRU) and the diagnostic cut-off value is 230 PRU.
Results: There was no statistically significant difference between CAD patients in the three treatment groups (clopidogrel vs. prasugrel vs. ticagrelor) in age (55±8y vs. 58±10y vs. 54±11y, p=0.55), prevalence of male sex (88% vs. 94% vs. 77%, p=0.41), smoking habits (40% vs. 33% vs. 46%, p=0.14), presence of diabetes mellitus (53% vs. 21% vs. 16%, p=0.06) and in the presence of multi vessel CAD (43% vs. 43% vs. 62%, p=0.53). Interestingly, subjects under clopidogrel treatment had increased PRU compared to subjects under prasugrel and ticagrelor treatment [204 (168 to 276) vs. 125 (52 to 155) vs. 50 (7 to 167), $p<0.001$)]. Importantly, subjects in clopidogrel group had significantly impaired FMD compared to subjects in prasugrel and ticagrelor groups (4.76±1.97% vs. 8.66±3.76% vs.

8.68±1.24%, p=0.002). Finally, in the total study population there was an inverse association between FMD and PRU (rho=-0.387, p=0.02).
Conclusion: Prasugrel and ticagrelor treatment compared to clopidogrel treatment, showed a greater inhibition of platelet activation in CAD patients after PCI with a parallel improvement in endothelial function. Further studies are needed to elucidate the impact of prasugrel, ticagrelor and clopidogrel treatment on vascular function and atherosclerosis progression.

P6495 | BEDSIDE
High and low platelet reactivity on clopidogrel, prasugrel and ticagrelor in acute coronary syndrome patients: insight from a large cohort

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Purpose: Dual antiplatelet therapy with a P2Y12 inhibitor is mandatory in acute coronary syndromes (ACS) undergoing angioplasty. New antiplatelet drugs prasugrel and ticagrelor offer more efficient inhibition compared to clopidogrel. Under P2Y12 inhibitor, platelet reactivity (PR) assessment can predict ischemic and bleeding events. The aim of our study was to compare PR of P2Y12 inhibitors in a real-world setting.
Methods: PR was prospectively assesed in consecutive patients with recurent ACS or undergoing high risk angioplasty. PR was measured 24h after last intake of clopidogrel (C) and prasugrel (P) and 12h for ticagrelor (T) by flow cytometry measured vasodilatator-stimulated phosphoprotein platelet reactivity index (VASP-PRI) and light transmission agregometry with ADP 20μM (LTA-ADP). High Platelet Reactivity (HPR) was defined as VASP-PRI >50% or LTA-ADP >65% (thresholds previously linked to clinical events). Low Platelet Reactivity (LPR) was defined as VASP-PRI <16% or LTA-ADP<40%.
Results: 619 patients treated with aspirin and C (n=269), P (n=241) or T (n=109) were included from 01/2011 to 07/2013. Mean age was 62±13y.o., 81% were men and 65% STEMI. HPR was more frequent with C compared to P and T and significantly more frequent with P compared to T (Table 1). At the opposite, LPR was significantly more frequent in patients treated with T. Clinical and biological characteristics were similar between patients on P and those on T, except for hypertension, BMI and prior history of STEMI. In multivariate analysis, the significant predictor of HPR with VASP was P (OR=0.13; CI [0.08–0.22]) or T (OR=0.01 [0.01–0.09]). The significant predictor of LPR with VASP was T (OR=3.37 [2.09–5.44]).

Table 1. Platelet reacitivy assessment

	HPR		LPR	
	VASP-PRI	LTA-ADP	VASP-PRI	LTA-ADP
Clopidogrel	48%	37%	7%	14%
Prasugrel	12%*	15%*	27%*	44%*
Ticagrelor	1%*#	2%*#	55%*#	72%*#

*p<0.05 vs clopidogrel, #p<0.05 vs prasugrel.

Conclusion: This observational biological prospective study confirms a more potent platelet inhibition of the new P2Y12 compared to clopidogrel, mainly T. The very high rate of LPR found with T does not match with the bleeding risk found in the PLATO trial.

P6496 | BEDSIDE
Dual antiplatelet therapy improves the levels of CD34+ progenitor cells exrpessing endothelial phenotype as well as their conjugates with platelets in patients with acute coronary syndromes

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Purpose: Platelets interact with CD34+ progenitor cells and CD34+ cells expressing endothelial phenotype (CD34+/KDR+), inducing their differentiation into mature endothelial cells. We investigated the levels of CD34+, CD34+/KDR+ cells and their conjugates with platelets, in peripheral blood of patients with an acute coronary syndrome (ACS) as well as the effect of dual antiplatelet therapy (DAPT).
Methods: We studied 20 ACS patients (12 males, age 65±12) before (Baseline) and at 5-days after the initiation of DAPT with aspirin 100mg/day and clopidogrel 600mg loading dose followed by 75mg/day (Follow-up). Thirty healthy volunteers (17 males, age 55±15) served as controls. The CD34+ and CD34+/KDR+ cell levels and the platelet-CD34+ and platelet-CD34+/KDR+ conjugates were determined in peripheral blood samples, before and after platelet activation with 100μM ADP, in vitro, (10min at 37°C), at Baseline and at Follow up. Measurements were performed by flow cytometry using appropriate fluorescently labeled monoclonal antibodies. Results are expressed as % in lymphomonocyte gate.
Results: The levels of CD34+ and CD34+/KDR+ cells in ACS patients at Baseline were significantly lower compared with controls (0.39±0.17% vs 0.78±0.4% and 0.04±0.01% vs 0.08±0.03%, respectively, P<0.01 for both comparisons). DAPT therapy significantly increased CD34+ as well as CD34+/KDR+ cells (from 0.39±0.17% to 0.67±0.39% and from 0.04±0.01% to 0.07±0.01%, respectively, P<0.01 for both comparisons). Importantly, the platelet-CD34+/KDR+ conjugates were lower at Baseline compared with controls either before (0.48±0.2% vs 1.3±0.8%, respectively, P<0.01) or after activation with ADP (0.90±0.23% vs 1.75±0.25%, respectively, P<0.01). At follow up, platelet-CD34+/KDR+ conjugates were increased compared with Baseline by 56.3% in the non-activated, and by 44.4% in the ADP-activated samples, P<0.05 for both comparisons).
Conclusions: The lower levels of CD34+, CD34+/KDR+ cells and platelet-CD34+/KDR+ conjugates in peripheral blood of ACS patients may represent an important defect of these patients towards vascular regeneration which is significantly improved after DAPT.

P6497 | BEDSIDE
Effect of dyspnea under ticagrelor on discontinuation and compliance to therapy in acute coronary syndrome patients treated with percutaneous coronary intervention

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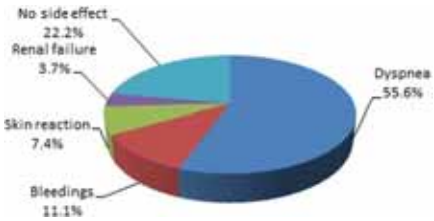
Purpose: Ticagrelor is a new P2Y12- ADP receptor antagonist which is superior to clopidogrel to prevent major adverse cardiac events (MACE) in acute coronary syndrome (ACS) patients. Dyspnea appears to be a common side effect of ticagrelor which could lead to drug non-compliance or discontinuation which are both associated with a poor outcome. We aimed to investigate the impact of ticagrelor-related dyspnea on both discontinuation and compliance to ticagrelor in ACS patients undergoing percutaneous coronary intervention (PCI).
Methods: We performed a multicenter prospective observational study enrolling ACS patients undergoing PCI and treated with ticagrelor. Clinical events including: MACE, bleedings and dyspnea were assessed at one month. Ticagrelor discontinuation and non-compliance and their causes were recorded.
Results: One hundred and sixty four patients were included among which a majority suffered from non ST-segment elevation myocardial infarction (NSTEMI) (48.4%). Overall 37 patients (22.6%) experienced dyspnea during the first month following the ACS. During follow-up, 27 patients (16.7%) discontinued ticagrelor. The main reason for ticagrelor withdrawal was drug-related dyspnea (55.6%). Discontinuation was the result of physician's decision in 26 patients (96.2%) and non-compliance was reported in only 1 patient. Ticagrelor was replaced by clopidogrel in 22 patients (81.6%).



Reason for ticagrelor discontinuation.

Conclusion: In the present study we observed that in ACS patients undergoing PCI and treated with ticagrelor, drug-related dyspnea is a frequent side effect (16.7%) and is the leading cause of drug discontinuation (55.6%). However, in most cases (81.6%) ticagrelor discontinuation was decided by a physician and the drug was replaced by clopidogrel to dual antiplatelet therapy.

ANTIPLATELET THERAPY: TRANSLATIONAL SCIENCE

P6499 | BEDSIDE
Determinants of cyclooxygenase-1-inhibition with aspirin in patients with stable coronary artery disease

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Purpose: Aspirin is widely used for secondary prophylaxis in patients with stable coronary artery disease (CAD), yet there is considerable variability in platelet inhibition. Low-dose aspirin inhibits the cyclooxygenase-1 (COX1) enzyme and measurement of serum thromboxane B2 (S-TXB2) is the most specific method for evaluating platelet inhibition with aspirin. We investigated independent determinants of COX1-inhibition with aspirin in a large cohort of stable CAD patients.
Methods: A total of 900 high-risk, stable CAD patients were included: 795 (88%) had a history of myocardial infarction, 250 (28%) had type 2 diabetes, and 170 (19%) had both. All patients received aspirin 75 mg daily and no other antithrombotic drugs. Compliance was carefully optimized, and the last aspirin dose was ingested exactly one hour before blood sampling. Blood for S-TXB2 analyses was collected in non-anticoagulated glass tubes and allowed to clot at 37 C for one hour to induce maximal platelet activation and TXB2 production. Serum was stored at -80 C until analyzed in duplicate by ELISA. Determinants of aspirin-induced COX1-inhibition were evaluated using multiple linear regression analyses.
Results: Optimal compliance was confirmed by very low S-TXB2 levels in all patients (median [25%;75%]: 0.97 [0.52;1.97] ng/mL). The results of regression

analyses were consistent, and the following six parameters were independent predictors of COX1-inhibition: Age, sex, body mass index, diabetes mellitus type 2, renal function (estimated glomerular filtration rate) and platelet count (all p-values <0.004). S-TXB2 levels were increased by 58% in males (p<0.001) and by 45% in patients with diabetes mellitus type 2 (p<0.001).
Conclusion: Low-dose aspirin inhibits platelet COX1 in patients with CAD, however we observed considerable inter-individual differences just one hour after ingestion of aspirin. Age, sex, body mass index, diabetes mellitus type 2, renal function and platelet count significantly affect aspirin-induced COX1-inhibition. Our findings may explain previous reports of reduced platelet inhibition with aspirin.

P6500 | BEDSIDE
Red blood cell and platelet microparticles in myocardial infarction patients

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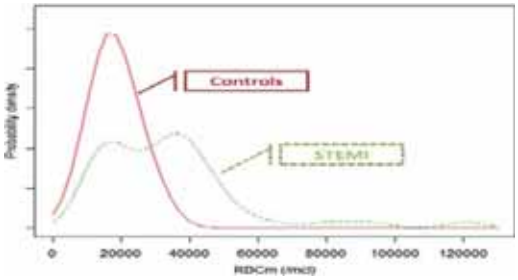
Background: Red blood cell and platelet microparticles (RBCm and PLTm, respectively) have drawn research attention as to their potential prothrombotic and vasoconstrictive effects in experimental settings. However, the relevance of circulating microparticles in clinical settings is largely undetermined.
Methods: Blood samples were drawn from consecutive STEMI patients after primary PCI and a matched cohort of healthy volunteers and circulating microparticles were quantified with a flow cytometric method. STEMI patients were followed for 6 months for a composite clinical endpoint. 51 STEMI patients (age 59.8±8.8 years) and 50 matched controls (age 56.2±9.2 years; p=0.155) were enrolled.
Results: RBCm concentration was 18,198±6,062 /μl in controls versus 33,740±21,169 /μl in STEMI patients (p<0.001). RBCm count was not correlated to total RBCs (standardized beta 0.018; p=0.861).
PLTm did not differ between cohorts (17,529±16,292 /μl in STEMI patients versus 14,372±6,211 /μl in controls; p=0.203). RBCm c-statistic was 0.832 (95% confidence interval 0.720 to 0.944), while PLTm prognostic value was not statistically significant (c-statistic 0.614, 95% confidence interval 0.444 to 0.784). In the multivariate analysis, RBCm concentration was independently associated with the clinical endpoint, after adjustment for age, ejection fraction, serum creatinine and presence of diabetes (adjusted p=0.034).



Conclusion: The present study demonstrates for the first time that erythrocyte microparticles are elevated in patients with STEMI treated with primary PCI, with levels approximately double those measured in a reference population of healthy volunteers, and their concentrations appear to be positively associated with adverse clinical events.

P6501 | BEDSIDE
Myeloid-related protein 8/14 is associated with increased platelet aggregation in patients with stable coronary artery disease

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Purpose: Recent studies suggest that myeloid-related protein 8/14 (MRP 8/14) may be implicated in the pathogenesis of coronary artery disease (CAD) and cardiovascular events. Furthermore, MRP 8/14 has been associated with thromboxane-dependent platelet activation in patients with non ST-elevation myocardial infarction. Importantly, the impact of MRP 8/14 on platelet aggregation in stable CAD patients treated with aspirin has not been investigated. The aim of the study was to investigate the association between MRP 8/14 and platelet aggregation in stable CAD patients. Furthermore, we aimed at investigating independent predictors of MRP 8/14.
Methods: We performed a cross-sectional study including 581 stable, high-risk CAD patients. Among these, 533 (92%) had a history of prior myocardial infarction, 148 (25%) had type 2 diabetes and 100 (17%) had both. All patients received 75 mg aspirin daily as mono antiplatelet therapy. Platelet aggregation was assessed by 1) multiple electrode aggregometry (MEA, Multiplate Analyzer) using arachidonic acid (AA) and collagen as agonists, and 2) the VerifyNow Aspirin Assay. MRP 8/14 and soluble P-selectin were measured by ELISA. Likewise, cyclooxygenase-1 inhibition was evaluated by measurement of serum thromboxane B2 using ELISA.
Results: MRP 8/14 was positively correlated with AA-induced MEA platelet aggregation (r=0.11, p=0.01). Additionally, MRP 8/14 was positively associated with serum thromboxane B2 (r=0.11, p=0.02), soluble P-selectin (r=0.10, p=0.03), body mass index (r=0.12, p=0.004), leukocytes (r=0.33, p<0.0001), high-sensitive C-reactive protein (CRP) (r=0.32, p<0.0001) and interleukin-6 (r=0.28, p<0.0001). MRP 8/14 levels were significantly higher in patients with type 2 diabetes than in non-diabetic patients (median [25%;75%]: 1.34 [0.94;1.92] vs. 1.05 [0.79;1.47] μg/mL, p<0.0001), and in patients without prior myocardial infarction than in patients with prior myocardial infarction (1.42 [1.04;1.95] vs. 1.10 [0.81;1.52] μg/mL, p=0.004). Prior myocardial infarction (p=0.04), high-sensitive CRP (p=0.02) and interleukin-6 (p=0.001) were all independent predictors of MRP 8/14, and additionally, a trend was seen for smoking (p=0.06). Compliance with aspirin was confirmed by low serum thromboxane B2 levels in all patients (median [25%;75%]: 1.07 [0.52;1.87] ng/mL).
Conclusion: High levels of MRP 8/14 were associated with increased platelet aggregation in stable, high-risk CAD patients. However, the association was weak suggesting limited impact of MRP 8/14 on the antiplatelet effect of aspirin.

P6502 | BEDSIDE
The effect of antiplatelet therapy on extra-cellular vesicles in blood of patients with acute coronary syndromes

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Purpose: Extracellular vesicles (EVs) play an important role in various pathologies, particularly in vascular disease. The purpose of our study was to analyze the antigenic composition of individual EVs isolated from the blood of patients with acute coronary syndrome (ACS), to explore the role of EVs of different cellular origin in atherosclerotic plaques maturation/rupture. In patients with ACS, we also assessed the effect of therapy on different EVs, predominantly on platelet-derived EVs.
Methods: We used monoclonal antibody- coupled, nanometer-sized magnetic particles to immune-captured CD31 and CD63-carrying EVs and analyze the expression of the exosomal marker CD63, the marker of different cellular origin CD31, and the platelet marker CD41 on EVs isolated from the blood of 10 patients with ACS and 15 healthy volunteers. For individual antigenic characterization of nano-sized blood EVs by means of flow cytometry we used an original method, described by us earlier (in press).
Results: In our pilot study we showed that there was significantly lower amount of captured by CD31 EVs co-expressing CD41 and CD63 in patients with ACS in comparison with healthy volunteers (Me [Q1;Q4], vesicles per microliter: 20.9 [10.01;31.35] vs 42.8 [29.8;52.1], p<0.05). We assumed that the difference in the amount of EVs expressing platelet-derived marker CD41 might be related to the standard antiplatelet therapy used in patients with ACS and confirmed the suppression of platelet activation upon the action of aspirin and clopidogrel.
Conclusions: We showed for the first time that patients with ACS had lower amount of EVs co-expressing CD31, CD41 and CD63 markers using a new method of individual assessment of extra-cellular vesicles in blood. The difference in the amount of EVs expressing platelet-derived marker CD41 confirmed platelet deactivation upon the standard antiplatelet therapy in patients with ACS.

P6503 | BEDSIDE
Platelet expression of transforming growth factor beta 1 is enhanced and associated with cardiovascular prognosis in patients with acute coronary syndrome

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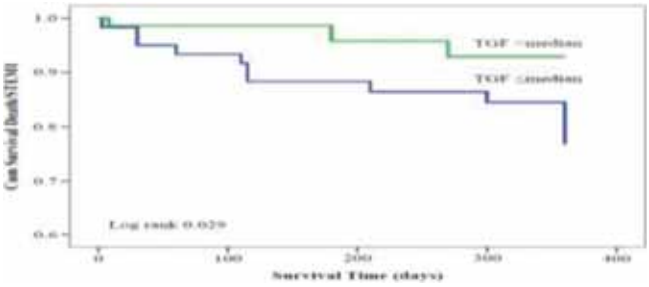
Background: Functional recovery and prognosis after acute coronary syndromes (ACS) are mainly driven by the extent of reperfusion injury and myocardial repair mechanisms. Transforming growth factor-beta (TGF-β) is critically involved in cardiac injury, repair and remodelling. In this study, we investigated the prognostic role of platelet TGF-β surface expression in patients with coronary artery disease (CAD).
Methods and results: Expression of TGF-β1 in platelets was investigated by flow cytometry among patients with ACS and stable CAD undergoing percutaneous coronary intervention (PCI). In a cohort study, platelet surface expression of TGF-β1 was measured in 299 patients with symptomatic CAD (stable CAD =145, ACS =154) at the time of PCI. The primary combined endpoint was defined as death and/or STEMI during 12-month follow-up. TGF-β1 surface expression was significantly elevated on platelets in ACS patients compared to patients with stable CAD (median MFI 13.4 vs. median MFI 11.7, p=0.003). During follow-up, lower expression of TGF-β1 was associated with all-cause mortality (median MFI 11.0 vs. median MFI 13.9, p=0.011) as well as for the combined endpoint of death



KM curve cumulative survival.

and/or STEMI, (median MFI 10.8 vs. median MFI 13.9, p=0.006). In multivariate analysis TGF-β1 expression was independently associated with the combined primary endpoint in the overall cohort (Hazard Ratio 0.31, 95% Confidence Interval 0.11-0.89, p=0.029) and was strongly associated with prognosis in ACS patients.
Conclusion: These findings highlight a potential role of TGF-β1 in ACS and indicate a prognostic value of TGF-β1 on clinical outcomes in patients with acute coronary syndromes. Large scale studies are warranted to further evaluate the regulatory mechanisms of platelet TGF-β1 expression- and its prognostic impact in CAD.

P6504 | BEDSIDE
Ticagrelor inhibits release of pro-inflammatory cytokines TNF and IL-6 during human endotoxaemia

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Purpose: In the PLATelet inhibition and patient Outcomes (PLATO) study, ticagrelor was associated with fewer pulmonary infection events and subsequent deaths but slightly higher inflammatory markers compared to clopidogrel. Ticagrelor and clopidogrel inhibit platelet P2Y12 receptors via different mechanisms and ticagrelor additionally is a weak inhibitor of reuptake of adenosine, which has numerous effects on innate immunity. We studied the effects of ticagrelor and clopidogrel on the innate immune responses of healthy volunteers.
Methods: 30 healthy volunteers were randomized to receive ticagrelor 90 mg bd (n=10), clopidogrel 75 mg od (n=10) or no antiplatelet medication (controls; n=10) for one week. E. coli endotoxin (LPS, 2 ng/kg) was then administered intravenously. Blood was sampled pre-treatment and over 24 hours post LPS. Platelet aggregation induced by ADP 30 μM was assessed by optical aggregometry. Platelet P-selectin expression and platelet-leukocyte aggregate formation were determined by flow cytometry. Plasma levels of cytokines were determined using cytometric bead array.
Results: After treatment, maximal platelet aggregation responses to ADP in the ticagrelor, clopidogrel and control groups were 12±6%, 31±26% and 81±24% respectively. After LPS exposure, ticagrelor and clopidogrel significantly reduced ADP-induced platelet P-selectin expression and platelet-monocyte conjugate formation compared to controls. LPS-induced increases in TNF were significantly attenuated by both ticagrelor (p=0.025) and clopidogrel (p=0.017), which reduced peak levels by 61% and 60% respectively compared to controls. Peak TNF levels correlated with indices of platelet reactivity (ADP-induced platelet aggregation [p=0.0096], P-selectin expression [p=0.026] and platelet-monocyte conjugate formation [p=0.024]). Ticagrelor also significantly attenuated IL-6 release (p=0.015), reducing peak levels by 43% compared to controls, whereas clopidogrel had a non-significant effect (p=0.15), with peak levels 28% lower than controls.
Conclusion: Ticagrelor inhibited release of pro-inflammatory cytokines TNF and IL-6 in a model of human sepsis. The similar effect of ticagrelor and clopidogrel, as well as the correlation between levels of platelet reactivity and TNF release, suggest that P2Y12 contributes to innate immune response and demonstrates anti-inflammatory effects of P2Y12 inhibitors.

P6505 | BENCH
Ticagrelor increases adenosine plasma concentration in patients with an acute coronary syndrome

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We aimed to investigate the impact of ticagrelor compared to clopidogrel on adenosine plasma concentration in acute coronary syndrome (ACS) patients.
Background: Ticagrelor is a novel direct acting P2Y12-ADP receptor blocker. The clinical benefit of ticagrelor compared to clopidogrel in ACS patients suggested non-platelet directed properties of the drug. Experimental and in-vitro experiment suggested that these pleiotropic properties of ticagrelor may be related to an interaction with adenosine metabolism.
Methods: We prospectively randomized 60 patients with an ACS to ticagrelor or clopidogrel. Adenosine plasma concentration (APC) was measured by liquid chromatography. To assess the mechanism of APC variation we measured adenosine deaminase activity, adenosine uptake by red blood cells (RBC) and cAMP production by cells that over expressing adenosine receptors. The VASP index was used to assess P212-ADP receptor blockade.
Results: Patients receiving ticagrelor had significantly higher APC compared with those under clopidogrel (1.5[0.98-1.7] vs 0.68[0.49-0.78] μM or with controls 0.6[0.5-0.8] μM; p<0.01). APC was not correlated with VASP (p=0.16). Serum containing ticagrelor inhibits adenosine uptake by RBC compared with clopidogrel or with controls (p<0.01). ADA activity was similar in serum of patients under both clopidogrel and ticagrelor (15[12.6-18.2] and 13.5[12-16] vs controls: 8[7.1-9] IU; p<0.01 for both groups). Serums of patients treated with clopidogrel or ticagrelor had no impact on adenosine receptors as measured by cAMP production (p=ns).
Conclusions: Ticagrelor increases APC in ACS patients compared to clopidogrel by an inhibition of adenosine uptake by RBC. This property over adenosine metabolism may participate in the so-called pleiotropic properties of the drug and in its specific side effects.

P6506 | BENCH
No effect of platelet supplementation to reverse the P2Y12 inhibitor ticagrelor: an in vitro study

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Purpose: Ticagrelor, a reversible P2Y12 inhibitor, is recommended for the treatment of acute coronary syndrome. Ticagrelor, as any antithrombotic therapy, exposes to bleeding complications. Currently, no antidote is available. Platelet transfusion, usually proposed as a reversal strategy for antiplatelet drugs, has been suggested to be inefficient since circulating ticagrelor as well as its active metabolite are likely to inhibit transfused platelets. However no data have been published yet.
We assess, in vitro, the efficacy of platelet supplementation to restore platelet aggregation inhibited by ticagrelor. Aspirin was used as a positive control.
Methods: Whole blood from eighteen healthy volunteers was spiked with ticagrelor (3.25μM, equivalent to the peak concentration after a 180 mg loading dose) or aspirin (25μM). Platelet aggregation was investigated with impedance aggregometry on whole blood and light transmission (LTA) on platelet rich plasma (PRP) using adenosine diphosphate (ADP 20μM) or arachidonic acid (AA 1mM) as specific agonists for ticagrelor and aspirin respectively. Platelet supplementation was defined as the addition of washed platelet suspension, corresponding to at least 60% of whole blood platelet count. Results are expressed in ohms or maximal percentage of aggregation for impedance and LTA, respectively.
Results: Ticagrelor strongly inhibited ADP-induced platelet aggregation compared to control either in whole blood (1.8 Ω vs. 8.8 Ω, p<0.05, n=6) or in PRP (14% vs. 77% p<0.05, n=6). Aspirin also inhibited AA-induced whole blood aggregation (1.3 Ω vs. 6 Ω, p<0.05, n=6). In aspirin-treated samples, platelet supplementation completely restored AA-induced platelet aggregation (9.8 Ω vs. 1.3 Ω, p=0.008). In contrast, in ticagrelor-treated samples, platelet supplementation failed to correct the antiplatelet effects of ticagrelor on ADP-induced aggregation both in whole blood (1.5 Ω vs. 1.3 Ω, p>0.05) and PRP (13% vs. 14%, p>0.05).
Conclusions: In this in vitro study, platelet supplementation failed to restore platelet aggregation following ticagrelor treatment whereas a complete correction was observed in aspirin-spiked samples. Our results support the hypothesis for an inefficacy of platelet transfusion to control bleeding in patients receiving ticagrelor.

P6507 | BENCH
Revacept (GPVI-Fc) alone or combined with rtPA improves outcome after stroke

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Background: Several antiplatelet drugs for the treatment of myocardial infarction or ischemic stroke with potent anti-ischemic effects have been developed, but all incur a significant risk of bleeding. In contrast, soluble glycoprotein VI (GPVI-Fc/Revacept) promises efficacy without increasing bleeding risk. In this study, we examined the effect of Revacept on thrombus formation after endothelial vessel wall injury and on experimental stroke in mice, and the combination with varying doses of recombinant tissue plasminogen activator (rtPA).
Methods and results: Platelet adhesion and thrombus formation after endothelial injury was monitored in the common carotid artery by intra-vital fluorescence microscopy, and was significantly decreased by 1 mg/kg Revacept IV, compared to Fc only. Stroke was induced in mice by a one hour-occlusion of the middle cerebral artery and consecutive reperfusion. 1 mg/kg Revacept IV applied immediately before reperfusion significantly improved functional outcome, cerebral infarction and edema compared to Fc only. There were no signs of increased intracranial bleeding. Revacept improved survival after stroke compared to placebo treatment. Binding of Revacept and von Willebrand factor (vWF) to bovine collagen I was determined by ELISA. Both Revacept and vWF bind to collagen, and Revacept competitively prevented the binding of vWF to collagen.

In contrast, treatment with standard doses of rtPA led to markedly increased risk of bleeding. Combinations of Revacept with decreasing doses of rtPA led to maintained efficacy, but decreased bleeding risk.
Conclusions: Revacept reduces arterial thrombus formation, improves functional outcome and reduces infarct volume and edema after ischemic stroke. Revacept not only prevents GPVI-mediated, but also vWF-mediated platelet adhesion and aggregate formation. Therefore Revacept might be a potent and safe tool to treat ischemic complications of stroke without increasing the risk of bleeding. The combination with markedly reduced doses of rtPA may be attractive for effective therapy with reduced risk.

P6508 | BENCH
Ticagrelor potentiates the anti-aggregatory effects of adenosine via A2 receptor stimulation

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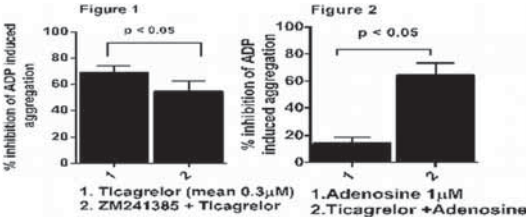
Purpose: Ticagrelor is a P2Y12 receptor antagonist which has been shown to inhibit adenosine uptake into erythrocytes. However the contribution of resultant potentiation of adenosine effect to the overall anti-aggregatory profile ticagrelor remains uncertain. We sought to evaluate ticagrelor-adenosine interactions in normal subjects and patients with ischemic heart disease.
Methods: Studies were performed both utilizing inhibition of ADP - induced aggregation in whole blood (2.5μM) and in platelet rich plasma (5μM ADP). Concentration response curves were constructed for ticagrelor in order to determine peri-threshold concentration for inhibition of platelet aggregation for ticagrelor alone. Interactions with adenosine were evaluated by 1. Inhibition of ticagrelor effects with A2 receptor blocker ZM241385 (100nM), while the effect of peri-threshold concentrations of ticagrelor on anti-aggregatory responses to adenosine was also determined.
Results: In whole blood, threshold concentration for ticagrelor anti-aggregatory effect was approximately 0.3μM, while the anti-aggregatory effects of higher concentration of ticagrelor were partially inhibited by ZM241385 (Fig. 1). In platelet-rich plasma, ticagrelor (mean 0.25μM) induced only 14±4% inhibition of aggregation. However, this peri threshold concentration of ticagrelor markedly potentiated the anti-aggregatory effect of adenosine (Fig. 2).



Conclusions: 1. Adenosine contributes to the antiaggregatory effects of ticagrelor primarily via A2 receptor stimulation 2. There is a synergistic relationship between ticagrelor and adenosine with regards to the inhibition of ADP induced platelet aggregation.

DELIVERING A PRIMARY PERCUTANEOUS CORONARY INTERVENTION SERVICE IN THE REAL WORLD

P6510 | BEDSIDE
Nation-wide real-life implementation of primary percutaneous coronary intervention strategy improves survival in patients with ST-elevation myocardial infarction

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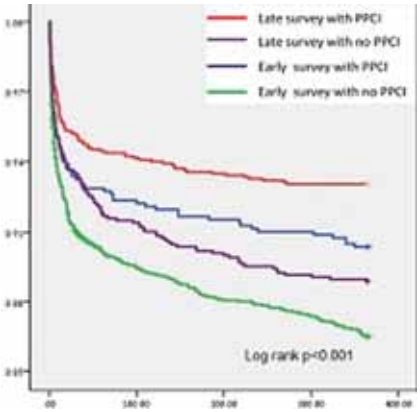
Background: The acute treatment of STEMI has changed dramatically during the passing decade with the establishment of primary PCI as the preferred approach for primary reperfusion.
Methods: We evaluated time-dependent changes in the clinical characteristics, management strategies, and outcomes of patients with ST elevation myocardial infarction (STEMI) enrolled in the biannual Acute Coronary Syndrome Israeli Survey (ACSIS) between 2000 and 2010. This population was divided into an early and late period and compared.
Results: A total of 5474 patients presenting with STEMI were enrolled and included in this analysis. Patients in the later period had a higher prevalence of hypertension, hyperlipidemia and obesity but were slightly younger (p for trend <0.001 for all) and had a lower rate of renal failure. The time leg form symptom onset to ER arrival had not changed (p=0.853). Patients tended to present with lower rates of heart failure as reflected by lower KILIP scores (p for trend <0.001). There was a dramatic change in the acute medical therapy, mainly a steep increase in rates of primary percutaneous coronary intervention (PCI) paralleled by a decrease in the use of fibrinolysis (p for trend <0.001). We found a significant decrease in un-adjusted mortality in later period. After adjustment to acceptable covariates, primary PCI was associated with a 30% reduction in 1 year mortality (HR 0.7, p=0.037).



1 year survival by survey and primary PCI.

Conclusion: In patients with STEMI, mortality has decline significantly during the last decade. This may have been attributed to lower rates of severe co-morbidities coupled with the implementation of primary PCI therapy.

P6511 | BEDSIDE
The role of general practitioners in treating patients with ST-segment elevation myocardial infarction in isolated areas

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Purpose: European guidelines for ST-segment elevation myocardial infarction (STEMI) encourage healthcare networks to increase rates of, and decrease delays to reperfusion. We examined the effects of training general practitioners (primary care physicians [PCPs]) with equipment for prehospital management of STEMI patients in remote areas.
Methods: A network for cardiac emergencies was set up in the French North Alps in 2002 and a permanent registry of STEMI patients has been kept since. In remote areas (>30 min access for ambulances), 24 local volunteer PCPs were trained and equipped (electrocardiogram [ECG] machine, fibrinolysis kit and automated external defibrillators [AEDs]) to deal with cardiac emergencies. In this study, when the central call dispatcher receives a telephone call from a patient reporting chest pain with a high probability of STEMI in such an area, he sends a mobile intensive care unit (MICU) with a emergent physician on board and asks the local PCP, if one is available, to manage the patient while awaiting arrival of the MICU. Patients were taken by MICU to the interventional cardiology hospital if the diagnosis of STEMI was confirmed. We report on patients who received care from a PCP before arrival of the MICU.
Results: Between 2005 and 2010, 4015 patients were included in the STEMI registry; 180 were in an isolated area in Haute-Savoie, of whom 140 were in an area with a participating PCP; 62 patients were treated by a PCP before MICU arrival. Twenty-seven of the PCP-treated patients underwent thrombolysis by PCP and 8 patients with ventricular tachycardia/fibrillation were shocked by PCP with an AED before MICU arrival. Mean times from call to thrombolysis were shorter when the patient was managed by the PCP versus MICU alone in a remote area: 45.0±25.5 min vs 62.4±23.4 min, respectively (p=0.003). A diagnosis of STEMI without contraindication to thrombolysis was confirmed in the hospital in 26/27 patients treated as such by the PCP (one patient was diagnosed with a Tako-Tsubo syndrome).
Conclusions: Our data suggest that PCP care of STEMI patients located in isolated areas is safe and efficient, with high rates of resuscitation and thrombolysis and a shorter time to perform thrombolysis. The rate of PCP intervention in our network needs to be increased in order to optimize management of such patients.

P6512 | BEDSIDE
Distance-related differences in critical times, protocol activation and mortality in a regional STEMI network

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Introduction: We aimed to study the differences in critical network times and mortality in STEMI patients presenting to hospitals belonging to the same STEMI network but located at different distances to pPCI center.

Material and methods: We studied 416 patients with STEMI who presented to a pPCI center (n=141) or to a hospital located in: zone 1 - <70 km from the pPCI center (101), zone 2 - 70-150 km from the pPCI center (n=81), or zone 3 - 150-250 km to the pPCI center (n=93), and we compared the following time intervals: (1) presentation time (PT), from onset of symptoms to presentation, (2) protocol initiation time (PIT), from presentation to STEMI protocol initiation, (3) Ischemic time (IT)- from onset of symptoms to repermeabilisation, and (4) door to balloon (DTB), from arrival in the pPCI center to balloon.
Results: PT showed no significant difference between the groups (183.08 min vs 199.1 min vs 166.7 min vs 161.95, p=0.4). PIT was significantly lower in zone 3 (61.66 min in zone 3 vs 92 min in zone 2 vs 107 min in zone 1, p=0.002). DTB time (from the door of the pPCI center to balloon) was significantly longer for patients presenting directly to pPCI center compared to those arriving from zone 1, 2 or 3 hospitals (86.96 vs 52.27 vs 39.94 vs 43.9 min, p<0.001), who found the cath lab already prepared when they arrived, as a result of phone activation. As a result, despite of the differences in distance to pPCI center, total IT was not significantly different between the groups (344 min in zone 1, 369 min in zone 2, 366 min in zone 3, and 340.26 min in pPCI center, p=0.2), and this was reflected in similar rates of mortality (3.5% in pPCI center, 3.9% in zone 1, 3.7% in zone 2 and 3.2% in zone 3).
Conclusions: A well organized STEMI network, as the one existing in zone 3 in our study, could shorten protocol initiation and DTB times, thus reaching similar ischemic times and presenting similar mortality rates with the centers located closer to the pPCI center. Early activation of the STEMI protocol could lead to superior results even in areas situated at longer distances to the pPCI center.

P6513 | BEDSIDE
Impact of health care system delay on one-year mortality in early versus late presenting STEMI patients undergoing primary PCI

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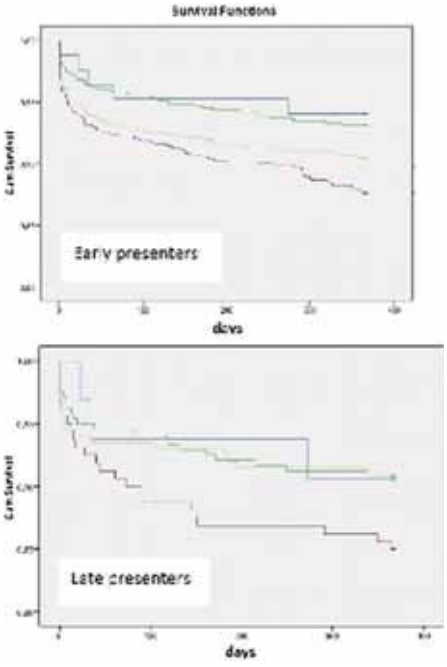
Purpose: Health care system delay, defined as time from first medical contact (FMC) to reperfusion, is predictor of adverse events in STEMI. Our aim was to assess the effect of system delay on one-year mortality in early (<2h after symptom onset) versus late (>2h after symptom onset) presenters.
Methods: The study included 2205 STEMI patients who underwent primary PCI within 12 hours of symptom onset, of whom 1573 were identified as early presenters, in a high-volume catheterization laboratory during the years 2010-2012. Between-groups comparison of Kaplan-Meier cumulative mortality curves for different time intervals of system delay was performed with log-rank test.
Results: One-year mortality was 9% in early presenters and 10.8% in late presenters (p=0.19). Median system delay was longer in early presenters (147 minutes, IQR 107-213 vs 132 minutes, IQR 99-182, p<0.001), while the total time to reperfusion was shorter (200 minutes, IQR 152-266 vs 382 minutes, IQR 300-508, p<0.001). A system delay of 0-60 minutes was associated with 3.8% one-year mortality in early presenters and 9.4% in late presenters, a delay of 61-120 minutes with 5.7% vs 9.2%, a delay of 121-180 minutes with 9.7% vs 9.5%, and if system delay was >180 minutes mortality rates reached 11.9% in early and 15% in late presenters. Log-rank test showed significant difference in Kaplan-Meier cumulative mortality curves for different time intervals of system delay in early, but not in late presenters (p=0.003 and p=0.261) (Figure).
Conclusion: Unlike in late presenters, the association between system delay and one-year mortality is significant in patients presenting early after symptom onset. The most pronounced increase in mortality appears to occur in early presenters with system delay beyond 120 minutes.



Kaplan-Meier curves.

P6514 | BEDSIDE
Short term cost-effectiveness of a regional STEMI network

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Purpose: Current economical restraints might have a detrimental effect on the implementation of STEMI networks. The aim of our study was to evaluate the short-term cost-effectiveness of a STEMI network in Catalonia.
Methods: Catalonia STEMI network was established in June 2009. It serves a population of approximately 7.500.000 inhabitants. Cost evaluation included hospitalization, procedure, and additional on-call personnel. Mean cost per patient was obtained according to treatment (primary PCI (pPCI), rescue PCI, fibrinolysis, and no reperfusion). In order to avoid price changes between years, same cost was used for both periods. Effectiveness was evaluated with the combined end-point of death, myocardial infarction, and stroke at 30-days. Data from the IAMCAT-III registry was used to evaluate the clinical effectiveness before the network. Single center prospective registry was used to evaluate the clinical effectivenes after the establishment of the network.
Results: Mean cost per patient according to reperfusion strategy was pPCI: 7.010€; fibrinolysis: 6.868€; Rescue PCI: 11.094€; No reperfusion: 7.200€. Implementation of the network modified the reperfusion strategies (pPCI 31% vs. 89%; Fibrinolysis 37% vs. 3%; Rescue PCI 11% vs. 4%; No reperfusion 21% vs. 4%). The composite endpoint in the pPCI group decreased from 9.7% vs. 6.6%. Due to a small sample size in the rescue PCI, fibrinolysis, and no reperfusion groups after the establishment of the network; the combined endpoint in the phase before it was used for both periods (fibrinolysis 15.5%, rescue PCI 10.7%; no reperfusion 19.1%). The strategy was cost-effective with a negative ratio for the combine endpoint (-4.336€), and 30-days mortality (-3.905€).
Conclusion: The Catalonian STEMI network is a cost-effective strategy in the short term. Further studies are needed to compare these results in different scenarios.

P6515 | BEDSIDE
Building population-based AMI management systems using telemedicine as a foundation pillar

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Primary PCI (PPCI), Pre Hospital thrombolysis and STEMI networks that have contributed to reducing mortality from AMI in advanced countries are lacking in developing countries. As a result, young adults succumb from AMI due to shortage of ambulance networks and from financial constraints. Telemedicine is an attractive modality that can hugely expand access to care and provide accurate and cost-effective solutions for AMI management. It may be the missing link that reduces barriers in AMI care between developed and developing countries.
Purpose: We report the commencement of a population-based AMI program that employs telemedicine innovations and protocols.
Methods: The study has begun a pilot program in up to 100 centers in South America. Goals of the study include: 1) Increase access to AMI care; 2) Increase accuracy of diagnosis; 3) Provide comprehensive AMI management; 4) Deliver cost-effective management. A hub and spoke, comprehensive AMI network has been designed that uses telemedicine as a founding platform for providing AMI care to vast populations. The strategy uses Primary PCI with door to balloon (D2B) time <90 min at hub sites and thrombolytic therapy with door to needle (D2N) times <30 min at spoke sites. Spokes are located between 5-250 miles from the hubs and often include small, rural clinics and facilities that have limited physician and hospital resources. A sophisticated, telemedicine platform enables immediate diagnosis, secure network, user interface and compatibility, quality assurance and database management. A dedicated network of expert cardiologists provides immediate EKG diagnosis and teleconsultation using the telemedicine platform and employing a combination of internet, fax modem and telephone networks.
Results: A comprehensive pilot program has been initiated at multiple sites using telemedicine protocols. Compulsive quality, cost-effectiveness and mortality data will be collected. Early data will be available for ESC 2014.
Conclusions: The study represents an innovative population-based initiative that employs telemedicine to improve AMI care in developing countries.

P6516 | BEDSIDE

Hospital outcome of STEMI admitted to hospitals with and without PCI-facilities: results of MIR-RLP

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Background: The German annual "Bruckenberger Report" documents mortality rates of myocardial infarction (MI) based on available ICD data with large differences between different federal states and increased mortality rate in Rheinland-Pfalz (RLP). Little is known if ICD data is reflecting real life MI-outcome.
Methods: In cooperation with the Ministry of Health RLP we have been conducting a Myocardial Infarction Registry (= MIR-RLP) enrolling consecutive patients with STEMI admitted to hospitals (29 with (PCI-hosp) and 23 without PCI facilities (non-PCI-hosp)) in RLP within 24h of symptom onset. MIR-RLP consists of 3 study phases: I. Documentation of STEMI treatment and outcome Nov 2012–Apr 2013; II. Analyses of phase I data and regional benchmark conferences May 2013–Oct 2013; III. Documentation of STEMI treatment and outcome Nov 2013–April 2014 compared to phase I. We present the phase I data on treatment and outcome of STEMI in RLP.
Results: A total of 873 patients with STEMI were enrolled into MIR-RLP. Data is presented for PCI- versus non-PCI hospitals.

Table 1

	All STEMI n=873	PCI-hosp n=770	Non-PCI-hosp n=103	p-value
Age (years)	64.5	64.0	67.7	<0.05
Female gender	31.6	31.7	31.1	ns
Prior MI	13.0%	12.4%	17.0%	ns
Diabetes	24.3%	24.2%	25.3%	ns
Admission via "911"	60.7%	65.6%	22.4%	<0.05
Self-admission	17.7%	13.8%	47.1%	<0.05
Sympt. - Reperf. (min/median)	199	197	314	<0.05
Cardiogenic shock	8.3%	8.7%	5.0%	ns
Primary PCI	98.3%	98.1%	100.0%	ns
Hospital death	9.1%	8.7%	12.6%	

Conclusions: MIR-RLP is the first consecutive myocardial infarction registry covering all consecutive STEMI patients of one entire federal state supported by its health ministry. The phase I data showed an overall hospital mortality rate of 9.1% in clinical practice despite the high rate of acute reperfusion treatment. MIR-RLP documented the additional time delay caused by first admission of STEMI patients to non-PCI hospitals probably accounting for the trend of higher mortality in these patients.

P6517 | BEDSIDE

Long-term results of pharmaco-invasive strategy for ST-segment elevation myocardial infarction treatment

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Purpose: Primary PCI is the preferred strategy of reperfusion in STEMI. But in real life many STEMI patients present to non–PCI capable hospital and often cannot undergo timely primary PCI due to expected logistic delays and therefore receive fibrinolysis. Current guidelines recommend transfer of all STEMI patients to PCI-capable center for coronarography with a view to revascularization within 24 hours after lysis. But the place of such pharmaco-invasive strategy of reperfusion in STEMI management system is not well defined. We evaluated the effectiveness of treatment of STEMI patients, using these two strategies of reperfusion in real world settings.
Methods: A retrospective analysis of treatment of 427 STEMI patients that underwent PCI at a single center from January 1, 2011 to December 31, 2011 was performed. All patients were divided into 2 groups depending on strategy of reperfusion: the first one – primary PCI (294 patients), the second one included 133 patients that underwent PCI after fibrinolysis (rescue and routine early coronary intervention) at non–PCI capable referral hospital. All patients received heparin, loading dose of aspirin and clopidogrel. In the primary PCI group the median time from symptoms onset to balloon was 160 minutes with an interquartile range of 110 to 230 minutes, 77.9% of patients were delivered directly to our center, the rest were transferred from the nearest hospitals. In the pharmaco-invasive group the median time from symptoms onset to needle was 95 minutes (the interquartile range of 70 to140 min), the median time from lysis to PCI – 11.5 hours (the interquartile range of 8.5 to17.0 hours). The study endpoints included in-hospital mortality and the rate of major adverse cardiac and cerebrovascular events (MACCE), defined as composite of death, myocardial infarction, stroke and repeat revascularization at a mean 27.2±5.4 months of follow-up.
Results: The in-hospital mortality was 4.4% in the primary PCI group and 5.2% in pharmaco-invasive group, p=0.805. There was no significant difference between the groups in the incidence of major bleeding. At 27.2±5.4 months of follow up the difference between the groups in the incidence of MACCE was also insignificant (12.6% in the first group and 18.0% in the second group had at least one MACCE, p=0.178).
Conclusions: The study demonstrates that in real world settings when timely primary PCI is not possible due to long transfer times to PCI-capable hospital a pharmaco-invasive strategy combining fibrinolysis with an obligatory use of PCI has short-term and long-term results that are comparable to those of primary PCI.

P6518 | BEDSIDE

Simultaneous computerised activation of the primary percutaneous coronary intervention pathway reduced out-of-hours door-to-balloon time but did not improve mortality

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Background: In July 2009 out of hours (OOH) activation of our primary percutaneous coronary intervention (PPCI) pathway changed from separate telephone calls by coronary care unit (CCU) staff to individual team members, to a simultaneous computer generated mobile phone alert activated by CCU – both in response to either a pre-hospital ambulance alert, or notification by Accident and Emergency (A+E).
Purpose: To assess the impact of the new protocol on door-to-balloon (DTB) times, in hospital and 1 year mortality.
Methods: Using the myocardial ischaemia national audit project (MINAP) database patients presenting OOH (defined as weekdays 5pm – 9am, weekends and bank holidays) to the two interventional sites in our teaching trust were categorised into two groups – pre (Group 1) and post (Group 2) the introduction of the computerised alert.
Results: A total of 1234 patients (mean age 61, 75% male) were included in the analysis. OOH PPCI was performed for 793 (64%) patients – 295 in Group 1 and 498 in Group 2 –with similar baseline characteristics. Unadjusted median DTB times were 92 minutes (interquartile range [IQR] 75-111) for Group 1 and 76 minutes (IQR 64-97) for Group 2 ($p<0.0001$). The proportion of OOH PPCI patients achieving DTB time ≤90 minutes increased from 48% (n=141) in Group 1 to 70% (n=349) in Group 2 ($p<0.0001$). Introduction of the computerised alert was associated with shorter DTB time on univariate analysis (odds ratio [OR] 2.6, 95% confidence interval [CI] 1.9-3.4, $p<0.0001$) and remained significant on multivariate analysis after adjustment for age, gender, ethnicity, admitting hospital, direct 999 admission, cardiac failure at presentation, cardiac arrest on admission, and previous coronary artery bypass grafting (beta coefficient -0.09, p=0.03 for linear regression and OR 2.8, 95% CI 1.6-5.0, $p<0.0001$ for logistic regression). In hospital mortality was 4.1% in Group 1 and 5% in Group 2 (p=0.60). All-cause mortality at 1 year was 6.1% in Group 1 and 9.9% in Group 2 (p=0.09). On regression analysis introduction of the new system was not related to any change in in-hospital mortality (OR 0.8, 95% CI 0.4-1.6, p=0.54) or 1-year mortality OR 0.59, 95% CI 0.34-1.04, p=0.07).
Conclusions: Simultaneous computerised activation of the PPCI pathway in Sandwell and West Birmingham reduced DTB times and significantly increased the number of OOH STEMI patients achieving a target DTB time of ≤90 minutes. However this did not translate into a change in pre discharge or 1 year mortality.

P6519 | BEDSIDE

ST segment elevation myocardial infarction (STEMI) network sustains low hospital mortality throughout the years in an emerging country location

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Background: Mortality in patients with STEMI has decreased considerably in developed countries due to widespread reperfusion and institution of STEMI networks. STEMI hospital mortality is still from 10 to 15% in non-developed regions. In emerging countries STEMI networks are few, with heterogeneous results, and information on yearly results are scarce.
Objectives: To demonstrate that the organization of a public STEMI network (usually with less resources) could produce immediate good results and sustain it throughout the years.
Methods: We analyzed 921 consecutive STEMI patients admitted to a Percutaneous Coronary Intervention (PCI) hub public Hospital in a large city from an emerging country, network organized as a Registry. The established protocol involved acute coronary syndrome training in all seven Emergency Rooms and 126 SAMU ambulances, utilization of a tele ECG system when necessary, lysis with tenecteplase (TNK) when call to balloon would be >90 minutes (pharmaco invasive therapy - PIT), systematic rapid transfer with immediate cath if rescue or elective cath within 24 hours if stable) or primary PCI (PPCI) if call to balloon <90'. Patients also received aspirin, clopidogrel, enoxaparin and statin and other adjuvants according to guidelines. Results from years 2010 to 2013 were eval-

uated, no transfer was refused and no case was excluded of intention to treat analysis. The STEMI protocol was modified only for utilizing half dosage of TNK in older than 75 years in 2013.
Results: All 921 consecutive patients were analyzed, ages from 25 to 93 years old, median age 57.9±11.4, 69.8% males overall. We treated 145 cases in 2010, 130 in 2011, 334 in 2012 and 312 cases in 2013. PIT was the mode of reperfusion in 81.0%, 84.4%, 86.0% and 89.0% of yearly cases respectively and no significant differences in age, gender, hypertension, diabetics (32.9, 29.2, 30.8 and 30.0% respectively) from 2010-2013. Transfer to PPCI time overall was 95', rescue cath median 8,4 hours and elective cath median 17,7 hours. Hospital mortality was 6,9, 8,4, 6,6 and 3,5% respectively.
Conclusions: The utilization of a STEMI protocol that emphasizes early reperfusion, either by lytics (with PIT strategy thereafter) or by PPCI, associated with contemporary adjuvants, in a large city of an emerging country, was associated with hospital mortality close to developed countries since its inception. The yearly results have been maintained and in 2013 attained its best result. STEMI networks adequately designed to meet its location needs, even in a public system of a non-developed country, maintain consistently good results.

HEART FAILURE ISSUES

P6521 | BEDSIDE
Development of a new biomarker-assisted score for reverse remodelling prediction in heart failure: the ST2-R2

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Background: Biomarkers have been used in heart failure (HF) mainly for diagnostic purposes, for prognostic prediction of outcomes (death and/or rehospitalisation), and more recently to guide therapy. Limited data exists regarding biomarker use to predict left ventricular (LV) function recovery or reverse remodelling.
Aims: a) To examine the value of ST2, NT-proBNP, high-sensitivity troponin T (hs-cTnT) and Galectin-3 relative to LV systolic function recovery and reverse remodelling in systolic HF; and b) To develop a clinical score for reverse remodelling prediction.
Patients and methods: 304 patients (79.6% men, mean age 66.1±12.3 years) with baseline echo (all baseline LV ejection fraction -LVEF- <40%) and biomarker measurement (ST2, NT-proBNP, hs-cTnT and Galectin-3) were included in the study. Ischemic aetiology accounted for 56.2% of patients. Mean baseline LVEF was 28±7%. Most patients were in NYHA class II (73%) or III (21.4%). Reverse remodelling was defined as: 1) LVEF increase ≥15 percentage points; or 2) LVEF increase ≥10 percentage points + reduction of LV end-systolic diameter (LVESDi) ≥20%, at 12 months.
Results: Reverse remodelling was observed in 104 patients (34.2%) during 1 year follow-up. Mean LVEF increase in patients with reverse remodelling was 21.9±7.9% and mean LVESDi reduction was 21±13.6%. In univariable logistic regression analysis factors associated with reverse remodelling were age (p=0.018), non-ischemic aetiology of HF (p<0.001), NYHA functional class (p=0.023), baseline LVEF (p=0.005), absence of LBBB (p=0.002), ST2 (p=0.004), NT-proBNP (p=0.005) and hs-cTnT (p<0.001), while HF duration achieved borderline significance (p=0.079). In multivariable analysis, ST2 remained the only biomarker associated with reverse remodelling. A simple score (the ST2-R2 Score) for use in clinical practice was developed with an AUC=0.79 for predicting reverse remodelling. The variables that comprised this score were: baseline ST2 <48 ng/mL, non-ischemic aetiology, absence of LBBB, HF duration <12 months, baseline LVEF <24%, and β-blocker treatment.
Conclusions: The ST2-R2 Score, which includes the novel biomarker ST2 and five conventional risk parameters, accurately predicts reverse remodelling in systolic HF patients. ST2 was the only of the four studied biomarkers independently associated with reverse remodelling as defined.

P6522 | BEDSIDE
Cardiac biomarker ST2 reflects haemodynamic stress in dilated cardiomyopathy: results from a prospective cohort study

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Purpose: The cardiac biomarker soluble ST2 (sST2) is associated with adverse outcome in heart failure (HF). In experimental studies, sST2 expression is induced by myocardial stress and pro-inflammatory stimuli. Determinants of sST2 levels in HF patients have not been well described. We assessed the associations between sST2 levels and haemodynamic parameters reflecting right and left ventricular pre- and afterload in patients with dilated cardiomyopathy (DCM).
Methods: We prospectively recruited 102 patients with left ventricular ejection fraction (LVEF) <40% and a diagnosis of idiopathic DCM based on patient history, echocardiography and coronary angiography. Work-up included right sided heart catheterisation. Subsequently, heart transplantation and death were recorded. Soluble ST2 was measured by a highly sensitive immunoassay. Determinants of sST2 were assessed by linear regression analyses.
Results: Population characteristics and their association with sST2 in uni- and multivariate analyses are presented in the Table. Levels of sST2 were higher in patients with severe symptoms (NYHA III-IV) even after adjustment for LVEF (p=0.02). In multiple regression, only gender, heart rate and right atrial pressure remained independent predictors of sST2. After a median of 3.6 years, 12 patients were dead or heart transplanted. Baseline sST2 was higher in these patients than in survivors (p=0.05).

Predictors of sST2

Variable	Baseline value	Univariate r	p-value	Multivariate β	p-value
Age (years)	51±14	–0.19	0.05	–0.44	0.66
Gender (% male)	73		0.003	2.39	0.02
Systolic BP (mmHg)	116±20	–0.28	0.004	–0.40	0.69
Heart rate (bpm)	75±16	0.55	<0.001	3.61	0.001
Right atrial pressure (mmHg)	7±5	0.44	<0.001	2.34	0.02
Mean pulmonary artery pressure (mmHg)	24±10	0.33	0.001	–0.92	0.36
Pulmonary capillary wedge pressure (mmHg)	15±9	0.36	<0.001	0.32	0.75
Cardiac output (l/min)	4.9±1.5	–0.35	<0.001	–1.10	0.27
Left ventricular ejection fraction (%)	26±10	–0.43	<0.001	–0.37	0.71
NYHA class III–IV (%)	25		<0.001	1.07	0.29

Conclusion: In DCM, sST2 is independently associated with an elevated heart rate and venous congestion. Our results imply that sST2 reflects haemodynamic decompensation in DCM.

P6523 | BEDSIDE
Risk assessment in elderly patients with septic shock: the role of biomarkers and hemodynamic parameters

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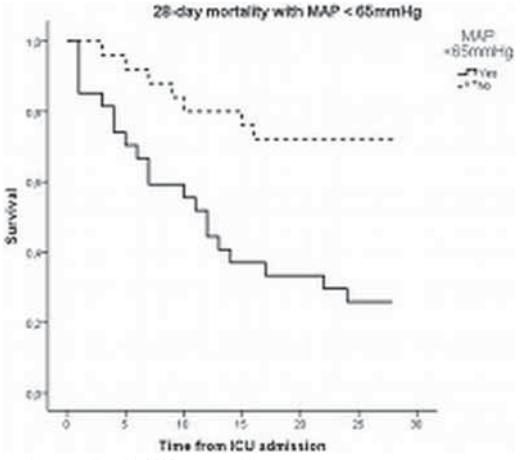
Purpose: Current guidelines suggest the assessment of hemodynamic parameters at admission for the risk stratification of patients with septic shock. Evidence so far is based on studies with middle aged patients. Therefore little is known about the management of elderly (≥65years) individuals.
Methods: Consecutive elderly patients (≥65y) treated for septic shock in the intensive care unit of one center (Marienhospital Herne, Ruhr University Bochum, Germany) were prospectively analyzed in this study. Hemodynamic parameters (mean arterial blood pressure (MAP), central venous pressure, central venous oxygen saturation, left ventricular ejection fraction) and cardiac biomarkers (hematocrit, troponin i, NTproBNP) at admission were evaluated in regard to their prognostic ability. Primary Endpoint was all-cause mortality within 28 days after admission.
Results: A total of 42 patients (23 male, 19 female) with a mean age of 74.6±6.0 years and a mean APACHE II score of 37.9±7.6 were enrolled in the study. 24 patients reached the primary endpoint. Non-survivors had significantly lower MAP (61.9±13.5 vs. 72.2±13.4, p=0.002) significantly higher NT-proBNP (8460±9186 vs. 1688±2062, p=0.007) and lactate (3.5±3.7 vs. 1.6±1.3, p=0.029). There were no significant differences regarding the left ventricular ejection fraction and troponin I between survivors and non-survivors.
MAP was the only hemodynamic parameter significantly predicting the primary endpoint (OR: 6.31, CI: 1.63–24.5, p=0.008).



28 day mortality with MAP <65 mmHg.

Conclusions: In our study population MAP at admission was the strongest predictor of short term mortality. NT-proBNP was associated with increased mortality in contrast to TnI which did not show any prognostic value.

P6524 | BEDSIDE

Preventing and managing cardiac disease in maternity – a model of care in a low resource set up

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Background: The spectrum of cardiovascular disease in pregnancy or in the postpartum period is changing and differs between countries. Worldwide, the numbers of patients who develop cardiac problems during pregnancy are increasing and this provides challenges for the treating physicians, due to the lack of evidenced-based data.
Methods: We report on an appropriate referral algorithm, disease presentation (n=225) and outcome of patients (n=152), with significant disease, warranting follow-up at a tertiary care facility, in a single-centre, prospective, ongoing study of African women presenting with cardiovascular disease in pregnancy or within 6 months postpartum. Clinical assessment, ECG, echocardiography and laboratory studies were performed at first assessment and follow-up at a dedicated Cardiac Disease and Maternity Clinic (CDMC).
Results: Of 225 consecutive women (mean age 28.8±6.4 years) presenting for the first time at CDMC 196 (86.7%) presented prepartum, with 73 women in modified WHO class I and 152 in modified WHO Class II-IV, with an ethnic background of 45% Black African, 32% Cape Colored, 15% White and 8% Indian/others. 12% were HIV positive. Diagnoses of the 152 patient cohort needing close follow-up were congenital heart disease (32%, 15 operated previously), valvular heart disease (26%, 15 operated previously), cardiomyopathy (27%) and 15% had other diagnoses. Women presenting in the postpartum period (n=30) presented in a higher New York Heart Association and modified WHO Class ($p<0.001$), had higher heart rates ($p<0.001$) and NTProBNP levels ($p<0.0005$). Of the 152 patients, 9 died within the 6-month follow-up period, with 8 dying >42 days postpartum. Perinatal death occurred in 1/152 (0.66%), translating to a perinatal mortality rate of 7/1000 live births.
Conclusion: The disease pattern was markedly different to that seen in the developed world. Rheumatic heart disease, cardiomyopathy and hypertensive heart failure are major problems, often complicated by HIV/AIDS as co-morbidity. Joint obstetric–cardiac care not only improved the survival rate of mothers presenting while pregnant, even those with complex diseases similar to that seen in the western world, but also that of their offspring. However, due to a lack of joint postpartum care, high mortality occurred in the postpartum period.

P6525 | BEDSIDE

Impact of isovolumic contraction time and isovolumic relaxation time on the change of left atrial volume after radiofrequency catheter ablation in patients with atrial fibrillation

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Introduction: It is known that large left atrial (LA) volume is a risk factor for the recurrence of atrial fibrillation (AF) after radiofrequency catheter ablation (RFCA). However, LA volume would not decrease despite successful RFCA in some patients. The aim of this study was to investigate the impacts of isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) on the change of LA volume index after RFCA for AF.
Methods: Subjects with nonvalvular AF who were scheduled for RFCA were enrolled. Transthoracic echocardiography was performed just before and 1 month after the RFCA in all subjects. LA volume was indexed by body surface area.
Results: A total of 292 patients (233 males, mean age: 57.1±11.6 years) were enrolled in this study. Post-ablation LA volume index (LAVI) was significantly decreased after one month compared to pre-ablation value (35.3±12.0 vs. 42.5±15.6 respectively, $p<0.001$). However, in 69 patients, post-RFCA LAVI was increased and the average difference between pre- and post-RFCA LAVI was 12.9mL/m^2. Patients with increased LAVI after RFCA had higher baseline IVCT, IVRT, and sum of both values than those with decreased LAVI (IVCT 51.1±28.8 ms vs. 40.4±28.7 ms, p=0.007; IVRT 56.5±34.4 ms vs 41.4±31.0 ms, p=0.001; sum of IVCT and IVRT 107.6±58.8 vs. 81.8±56.5, p=0.001, Fig. 1). The area under-curve of ROC curve was 0.648 for IVRT ($p<0.001$).
Conclusions: The IVCT and IVRT values could be predictors for paradoxical increase of LA volume despite successful RFCA in patients with atrial fibrillation.

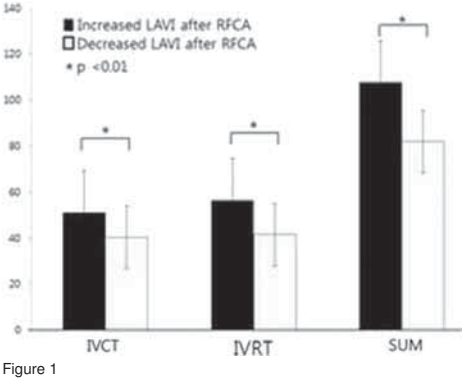

Figure 1

P6526 | BEDSIDE

The association of pulse transit time and left ventricular ejection fraction in patients with chronic heart failure

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Purpose: The aim of this study was to determine the association of pulse transit time (PTT) and left ventricular systolic function in patients with chronic heart failure (CHF).
Methods: 131 patients with CHF (51 females and 80 males, mean age was 59.2±8.6 years) were studied. 10 patients had functional class I of CHF, 50 – Class II, 67 – Class III, 4 – Class IV according to NYHA classification. Causes of CHF were: arterial hypertension (AH) in 13 patients, coronary artery disease (CAD) – 7, CAD and AH – 111 patients. 35 patients had diabetes mellitus. Patients were treated according to ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure, 2012. Left ventricular ejection fraction (LVEF) was 58.5±12.1%. 32 (24.4%) patients had LVEF<50%. Pulse transit time and the circadian rhythm of PTT were determined during 24-hour ABPM using MnSDP-2 and MnSDP-3 BPLab devices.
Results: Mean values of PTT were 107.4±25.4 milliseconds (ms) in 24-hours, 106.5±27.3 ms – in daytime, 110.3±30.5 ms – in nighttime. Mean 24-hours and mean daily values of PTT correlated with LVEF (R=-0.3, p=0.001 and R=-0.35, $p<0.001$, respectively). Mean values of PTT in 24-hours and in daytime were higher in patients with CHF with preserved LVEF (119.1±30.5 ms vs. 103.7±22.9 ms and 121.7±33.3 ms vs. 100.9±22.3 ms, respectively, p=0.005 and $p<0.001$). The degree of nocturnal RTT reduction was ≥0% in 62 (47.3%) patients. Moreover, the degree of nocturnal RTT reduction ≥0% was detected more frequently in patients with CHF with reduced left ventricular ejection fraction (75.0% patients vs. 43.4%, respectively, p=0.04).
Conclusions: Left ventricular ejection fraction is inversely proportional to the degree of nocturnal pulse transit time reduction. Further studies are required in order to assess the clinical significance of circadian changes in arterial stiffness indicators.

P6527 | BEDSIDE

GSTO1*Asp/GSTO2*Asp haplotype confers increased risk of chronic heart failure

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Background: Glutathione S-transferase omega-1 and 2 have a unique range of enzymatic activities, including the regeneration of ascorbate by their dehydroascorbate reductase activitie and act as a glutathione-dependent S-thioltransferase.Since these enzymes could have a protective role from oxidative damage, the question of whether two glutathione S-transferase omega polymorphisms confer the risk of chronic heart failure (CHF) was addressed.
Methods: rs4925 (Ala140Asp) of glutathione S-transferase omega-1 and rs156697 (Asn142Asp) of glutathione S-transferase omega-2 polymorphisms in 119 patients with chronic heart failure and 155 controls were assessed.
Results: Presence of one mutant GSTO1*Asp or GSTO2*Asp did not contribute independently towards the risk of CHF. However, homozygous carriers of mutant GSTO2*Asp genotype demonstrated 3.35-fold enhanced risk of CHF development in comparison to persons with wildtype GSTO2 Asn/Asn genotype (95% CI=1.19-9.39; P=0.021). Haplotype analysis revealed that homozygous carriers of both mutant GSTO1*Asp/GSTO2*Asp haplotype exhibited 11.14-fold enhanced risk of CHF (95% confidence interval = 1.38-90.23; P=0.024). Regarding the distribution of particular glutathione S-transferase omega genotype among various NYHA classes, the highest frequency of mutant GSTO1*Asp and GSTO2*Asp alleles were found in NYHA IV patients.
Conclusion: Based on results obtined it may be concluded that that GSTO2*Asn142Asp polymorphism could play an important role as a risk factor for the development of CHF.

P6528 | BEDSIDE

Features of electrocardiogram and echocardiography in patients with cardiac involvement of myasthenia gravis

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Purposes: Myasthenia gravis (MG) primarily affects not only skeletal muscle but

also heart muscle through the production of autoantibodies. Cardiac involvement is rare, but accompanies with poor prognosis. In the present study, we aimed to clarify the features of electrocardiogram, echocardiography, and clinical course in patients with MG.
Methods: Of 174 patients who diagnosed as MG between 2001 and 2012 in our hospital, we retrospectively analyzed 84 patients who were examined both by electrocardiogram and echocardiography. Of the 84 patients, 32 patients were excluded for having other underlying disease such as hypertension, ischemic heart disease, or chronic kidney disease. We also investigated the clinical course of these patients from diagnosis to 2013.
Results: Thirty one (56.5%) had ECG abnormalities: 19% had atrial fibrillation; 15% had atrio-ventricular block; 53% had non-specific ST depression; and 50% had negative T waves. There was no difference in age and sex between normal ECG group and abnormal ECG group, but the rate of administration with steroids and anticholinergic agents was higher in the abnormal ECG group. No cardiac death was observed in normal ECG group. Four (4.7%) patients had decreased ejection fraction (below 55%) and they all had ECG abnormalities, in which the mean (standard deviation: SD) duration from the onset of MG was 10.5 (9.8) years, and the mean (SD) ejection fraction was 34.7 (7.2) %. Two patients had thymoma and underwent thymectomy. Of the 4, 1 patient died of colon cancer. The other 2 patients were started to be treated with immunosuppressive agents because of cardiac dysfunction with good clinical course. However, one had died due to acute decompensated heart failure approximately one month after self-discontinuation of immunosuppressive agents.
Conclusions: ECG abnormalities, especially atrial fibrillation, were commonly observed in patients with MG. Of those with ECG abnormalities, an additional echocardiographic examination may be useful for the detection of cardiac involvement of myasthenia gravis as this may help an early detection and thus timely treatment, since this cardiomyopathy associated with MG has poor prognosis but can be treatable.

P6529 | BEDSIDE
Invasive exercise hemodynamic evaluation in LVAD patients: A new index for progressive aortic regurgitation

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Purpose: LVAD implantation in patients with advanced HF is clearly associated with functional improvement together with improved survival. However, the magnitude of benefit varies considerably, likely reflective of multiple underlying contributors. The central hemodynamic response to exercise in LVAD is not well characterised, and we hypothesised that this may represent one source of functional variability. Furthermore the impact of developing LVAD related hemodynamic complications such as aortic regurgitation (AR) and right heart failure (RHF) could also impact on functional changes. We therefore aimed to test the hemodynamic response in LVAD patients and to correlate these with functional capacity and the presence of progressive AR or RHF.
Methods: 39 patients (mean age 44±15yrs) with a 3rd generation LVAD underwent symptom limited invasive hemodynamic testing during right heart catheterisation. 19 patients were also followed up with serial echocardiography and 6 minute walk testing.
Results: Exercise in LVAD patients was associated with a modest rise in total cardiac output, with a non-signficant rise in LVAD output (Table). PA and PCWP pressures both increased significantly. Echocardiographic evidence of progression in AR grade (≥1) was evident in 5 patients over the post RHC follow-up period. In these patients there was a higher peak mean PA pressure (27±6 mmHg) compared to those without progressive AR (20±5 mmHg $p<0.05$). Exercise hemodynamics were not related to 6MWT.

Exercise hemodynamics in LVAD patients

	Cardiac output (CO) L/min	MAP mmHg	PAPm mmHg	PAWP mmHg	PAO2sats %	LVAD CO L/min
Baseline	5.3±1.4	82±13	21±8	12±6.0	65±8.3	5.1±1.3
Peak exercise	7.4±2.4	94±15	35±8	23±7.1	39±15.8	6.1±1.2
P value	<0.001	<0.001	<0.001	<0.001	<0.001	p=0.23

Conclusion: Invasive exercise hemodynamic testing provides novel insights into integrated circulatory performance after LVAD. In particular exercise hemodynamic testing may provide a means of early detection of developing aortic regurgitation after LVAD.

P6530 | BEDSIDE
Predictive value of delayed-enhancement magnetic resonance imaging in recent-onset dilated cardiomyopathy

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Introduction: Finding of delayed enhancement (DE) in the left ventricle on magnetic resonance imaging (MRI) predicts poor clinical outcome in patients with chronic dilated cardiomyopathy (DCM). Similar predictive value of DE has not yet been established in the patients with recent-onset DCM.
Methods: MRI was performed in 101 consecutive patients with recent-onset idiopathic DCM (age, 44±13 years; men, 71%; LVEF, 24±6%; LVEDD 67±6 mm; NYHA 2.9±0.8; duration of symptoms, 7±6 weeks). The patients were followed for a median of 2.5 years (IQR, 1.1 to 3.6). Observed cardiovascular events were related to baseline clinical characteristics, levels of cardiac biomarkers and the presence of any DE in the left ventricle.
Results: DE was present in 65 patients. During the follow-up, 10 patients died due to heart failure-related causes; 12 underwent urgent heart transplantation; 8 had implanted a ventricular assist device; and another 16 were rehospitalized for worsening of heart failure. Presence of any DE in the left ventricle was the strongest predictor of a combined endpoint of the above clinical events (hazard ratio [95% CI], 3.5 [1.2 to 10], P=0.02). In the non-transplanted patients, DE at baseline was associated with worse functional class at the end of the follow-up (NYHA, 2.1±0.9 vs. 1.7±0.7, P=0.03).
Conclusion: Presence of DE in the left ventricle seems to be a reliable marker of poor clinical outcome in patients with recent-onset idiopathic DCM.

P6531 | BENCH
Myocardial tetranectin levels are associated with cardiac fibrosis and serum concentrations are reduced in heart failure patients

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Purpose: Proteomics discovery work (2D-DIGE and mass spectrometry) using coronary sinus serum from asymptomatic hypertensive patients with low and high risk for future development of heart failure resulted in the identification of Tetranectin as a potential biomarker candidate. The precise functional role of Tetranectin is yet to be defined but its expression levels have previously been shown to increase within the extracellular matrix during development and disease whilst levels within the circulation decline. The purpose of this study was to validate the proteomics discovery, quantify serum levels of Tetranectin in a heart failure population, and to begin to assess the disease relevance of this novel protein within the heart.
Methods: This study conformed to the principles of the Declaration of Helsinki of the World Medical Association. Two patient cohorts were used for this study. Firstly, serum was collected from a validation cohort (n=100) of asymptomatic hypertensive patients (n=60) and heart failure patients with preserved ejection fraction (n=40), and were analysed for Tetranectin levels using ELISA. Secondly, myocardial tissue samples were procured during cardiothoracic surgery (n=38), and were analysed for gene expression levels of Tetranectin and the fibrosis related genes collagen type-1 and collagen type-3 using quantitative real-time PCR.
Results: In the validation cohort, Tetranectin was found to be significantly reduced in heart failure serum samples ($p<0.001$). Within human myocardial tissue samples Tetranectin gene expression levels significantly correlated with both collagen sub-types, collagen 1 ($r=0.50$, $p<0.01$) and collagen 3 ($r=0.48$, $p<0.01$).
Discussion: The proteomics approach identified the protein Tetranectin as a candidate biomarker of heart failure. Furthermore, we demonstrate for the first time that Tetranectin is expressed within human cardiac tissue, and its levels correlate with the degree of tissue fibrosis observed. Further work to explore the potential role of Tetranectin as a novel diagnostic and therapeutic for heart failure should be undertaken.

HEART FAILURE BASICS

P6533 | BEDSIDE
The interval-force relationship predicts mortality of cardiac patients

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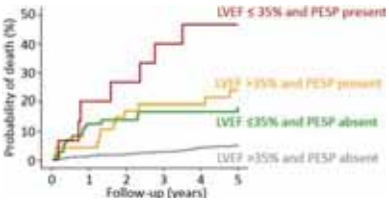
Purpose: Due to alterations in intracellular calcium cycling, failing myocardium is characterized by a steeper-than-normal interval-force relationship. This results in enhanced post-extrasystolic blood pressure potentiation (PESP). This study prospectively tested the association of PESP and mortality in cardiac patients.
Methods: 941 consecutive patients with acute myocardial infarction were enrolled and followed up for five years. Primary outcome was 5-year all-cause mortality. Patients underwent non-invasive 30-minute recordings of ECG and continuous blood pressure. PESP presence was defined as first post-ectopic pulse wave amplitudes larger than the mean of the subsequent nine pulse waves. Ventricular premature complexes (VPCs) suitable for PESP quantification were present in 220 patients. PESP was present in 62 patients. Patients without suitable VPCs were classified as PESP absent.
Results: 72 patients died during follow-up. Under univariable analysis, PESP was a significant predictor of death ($p<0.001$). Under multivariable analysis, PESP ($p<0.001$), GRACE score ($p<0.001$), and LVEF ($p<0.001$) were independently associated with mortality (with hazard ratios of 3.2, 2.6, and 4.7, respectively). PESP and LVEF were independent predictors, with the highest mortality risk in patients with both pathological PESP and LVEF (see Figure).
The finding was reproduced in an unrelated cohort of 146 heart failure patients.

Moreover, in a cohort of MI survivors with atrial fibrillation, a PESP-like parameter calculated from blood pressure patterns resulting from short-long-sequences was associated with a hazard ratio of 4.88 (p=0.017) for 5-year mortality.



Conclusion: The interval-force relationship is a powerful non-invasive means to assess the mortality risk of cardiac patients.

P6534 | BEDSIDE
Association of aortic stiffness with myocardial fibrosis in heart failure is disease specific: findings in patients with ischaemic and non-ischaemic cardiomyopathy

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Introduction: Myocardial fibrosis is the uniform pathophysiological substrate of failing heart; replacement fibrosis is the hallmark of ischemic heart disease (IHD), whereas interstitial myocardial fibrosis is characteristic for non-ischemic cardiomyopathies (NICMs). We examined association between aortic stiffness and measures of myocardial fibrosis by cardiovascular magnetic resonance (CMR) in patients presenting with symptoms and signs of HF, and whether these differ due to underlying etiology of cardiac impairment.
Methods and results: Consecutive 377 patients underwent CMR assessment of cardiac volumes and function, myocardial replacement fibrosis by late gadolinium enhancement (LGE) and interstitial myocardial fibrosis by T1 mapping. Central aortic stiffness was measured by pulse wave velocity (PWV). Patients with IHD (n=160) and NICMs (n=217) were compared to 48 asymptomatic and normotensive controls. Groups were similar for age and gender with greater representation of cardiovascular risk factors in IHD group. Compared to controls, both patient groups had significantly raised PWV, native T1 and extracellular volume fraction (ECV) ($p<0.01$). Patients with NICM had higher native PWV, T1, extracellular volume fraction (ECV) compared to IHD. In IHD, PWV was related to cardiovascular risk factors and native T1, whereas in NICMs, PWV was associated with native T1 and female gender. In IHD, native T1 was associated with the presence or type of LGE were not associated with PWV.

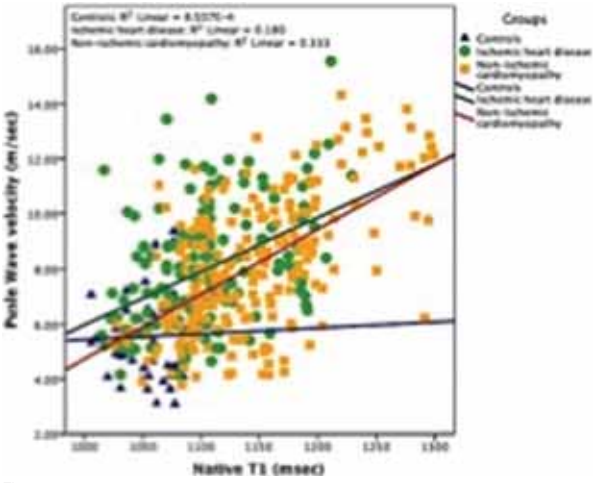

Figure 1

Conclusions: In symptomatic patients with HF, PWV is primarily associated with increase in diffuse interstitial but not replacement myocardial fibrosis, irrespective of the underlying etiology. This relationship is stronger in NICMs, and also gender specific.

P6535 | BEDSIDE
Chicken or egg? Changes in fluid retention before and after onset of atrial fibrillation in patients with chronic heart failure

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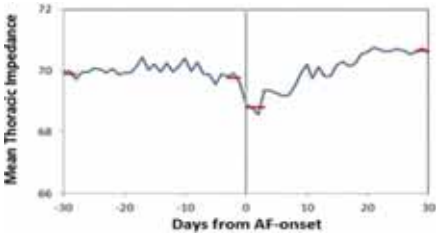
Atrial fibrillation (AF) is common in heart failure (HF) and associated with a worse prognosis. While it is recognized that AF-onset and worsening HF may trigger each other, detailed characteristics of this interrelation remain to be established. We monitored fluid retention by means of intrathoracic impedance (Z) to analyse the AF-HF interaction.
Methods: We studied 836 HF patients (EF 26±8) with an ICD or CRT-pacemaker (follow-up 15±4 months). AF-onset was defined as the first incidence of AF with a duration >6h/day which was not preceded by any AF in the 30d before. Daily values of Z, heart rate (night time) and the percentage of biventricular stimulation (%BIV) were recorded by the device. 3-day averages at 4 weeks and 3 days before AF-onset, as well as 3 days and 4 weeks after AF-onset were compared (Figure, bold lines).
Results: n=118 had an AF-onset episode lasting for median 1 day (IQR 1, 11). There was no significant Z-change 30 days prior to AF-onset (0 Ohm (95% CI -0.7, 0.7). From 3 days prior compared to 3 days post AF-onset, Z decreased by 1.0 Ohm (95% CI -1.6, -0.3, $p<0.01$; Figure) indicating increased fluid retention. This change was larger in subjects with higher heart rate and lower %BIV during AF (-1.5 (95% CI -2.7, -0.4), $p<0.01$). Hospitalization for HF was more common during the 30 days after (n=7) compared with before (n=1) AF-onset (p=0.03). Z increased from 3 d to 4 weeks after AF onset by 1.4 Ohm (95% CI 0.53, 2.29), $p<0.01$.



Conclusions: In this large group of HF patients no significant increase in fluid retention as a trigger of AF-onset was observed. In contrast, AF onset was associated with an immediate increase of fluid retention and an increased risk for subsequent HF hospitalization. Our data indicate a larger impact of AF-onset on worsening HF than vice versa.

P6536 | BEDSIDE
Galectin-3 and myocardial fibrosis at cardiac magnetic resonance in nonischaemic dilated cardiomyopathy

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Purpose: Left ventricular (LV) remodelling is related to worse outcome in nonischaemic dilated cardiomyopathy (DCM). LV fibrosis, assessed by late gadolinium enhancement (LGE) at cardiac magnetic resonance imaging (MRI), is a marker of LV remodelling, and helps in risk stratification in DCM. Galectin-3 has been recently shown to participate in tissue fibrogenesis and to be useful as prognosticator in heart failure. Our aim was to investigate the relationships between galectin-3 circulating level and myocardial fibrosis at cardiac MRI in nonischaemic DCM patients.
Methods: Eighty-eight patients were enrolled (males 72%, age 59±13 years), with a diagnosis of nonischaemic DCM by World Health Organization criteria. All patients underwent a comprehensive clinical assessment, biohumoral characterization including galectin-3 assay, and cardiac MRI, with LGE assessment of myocardial fibrosis.
Results: Median galectin-3 value was 14.5 ng/mL (IQR 12.4-19.0 ng/mL). In the whole population, galectin-3 levels were positively correlated with c-reactive protein (R 0.40, $p\leq0.001$), troponin I (R 0.41, $p\leq0.001$) and N-terminal pro-brain natriuretic peptide (R 0.37, $p\leq0.001$) plasma levels; a negative correlation was observed with renal function, expressed as estimated glomerular filtration rate (Cockroft-Gault, R 0.44; $p\leq0.001$). LGE was detected in 56 (64%) patients. Patients with LGE had higher galectin-3 levels than those without (16.4, 12.2-21.5, vs 13.3,12.3-17.0 ng/mL, p=0.038). Among univariate predictors of LGE presence (galectin-3, body mass index, disease duration, arterial hypertension, left and right ventricular ejection fraction), galectin-3 maintained its predictive value (OR 1.174 [1.048-1.352]; p=0.013) at multivariate analysis, together with arterial hypertension (OR 3.726 [1.151-13.693]; p=0.034) and disease duration (OR 1.018 [1.006-1.034]; p=0.010). At ROC analysis the optimal galectin-3 cut-off for LGE prediction was 14.6 ng/mL (AUC 0.609, sensitivity 59%, specificity 69%).
Conclusions: Galectin-3 is associated with myocardial replacement fibrosis assessed by LGE at MRI, in patients with nonischaemic DCM. This result supports

the hypothesis that galectin-3 is involved in cardiac fibrosis and remodelling, and that its assay may help to select high risk DCM patients.

P6537 | BEDSIDE
Pattern of ubiquitin expressions depends on advancement of heart failure in patients with idiopathic dilated cardiomyopathy

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Background: The ubiquitin–proteasome system is responsible for degradation of most cellular proteins and plays an essential role in nearly all aspects of cell function. Ubiquitin (UBI) conjugation of proteins is critical for cell homeostasis and contributes to both cell survival and death. Ubiquitination of protein leads to their proteasomal degradation or less frequently to autophagy or plays non–proteasomal cellular role. Aim: Evaluation of UBI expression (UBIEx) as a feature of heart failure (HF).
Methods: Endomyocardial tissue samples of left ventricle wall were obtained from 60 pts (85% of males, mean age 46±14 years) with clinical symptoms of HF (LVEF<45%). UBIEx and localization were investigated in histological sections by immunohistochemical method with use of anti-UBI (DAKO) antibody and Western-blotting method (W-B). Deparafinized sections stained with hematoxylin-eosin and Trichrom Masson were assessed in terms of histopathology including cardiomyocyte hypertrophy (CH) and tissue fibrosis. CH and fibrosis were assessed using morphometric software.
Results: Investigation of UBIEx in immunohistochemical and W-B reveled four groups of myocardial tissue samples: type A, normal, gentle staining of UBI in cardiomyocyte cytoplasm (9pts/15%); type B, increased, intensive staining in cardiomiocyte cytoplasm (24pts/40%); type C, increased, intensive staining in cardiomyocyte cytoplasm and nucleus (19pts/32%); and type D, decreased or lack of UBI staining (8pts/13%). Analysis showed different patterns of UBIEx with statistical significance or tendency between all groups according to LVEF, LVEDD and NT-pro-BNP, fibrosis and CH (see table).

UBIEx	LVEF [%]	LVEDD [mm]	NT-pro-BNP [pg/dl]	Fibrosis [% of area]	Cardiomyocyte [μm]	Cardiomyocytes hypertrophy (CH)
Type A	44.8±10	58.3±6	772±234	13.2±9.0	21.3±6.6	Isolated, compensatory
Type B	37.6±11	61.8±8	1331±456	16.4±11.9	26.6±7.1	All, compensatory
Type C	27.2±7	66.2±5	1562±822	26.8±14.8	28.6±7.1	Degenerative CH
Type D	27.5±7	67.3±5	2155±1180	26.9±8.7	29.4±6.4	Degenerative CH
P	0.002	0.1	0.02	0.09	0.06	

LVEF: left ventricle ejection fraction; LVEDD: left ventricle end diastolic diameter.

Conclusions: Different types of UBIEx corresponds with changes in cardiomyocyte structure. UBIEx especially type C and D is associated with CH, higher rate of fibrosis and NT-pro-BNP level, increased LVEDD and lower LVEF.

P6538 | BEDSIDE
Low birth weight and etiology of heart failure at adult age – can NTproBNP provide additional data?

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Purpose: It is well known that antenatal conditions and genetic structure determine postnatal growth, with proven influence on susceptibility to adult cardiovascular diseases, especially ischemic heart disease. Conversely, the influence of fetal growth restriction (evident by low birth weight-LBW) on non-ischemic cardiomyopathies (CMP) in adults has not been studied. We studied our center's heart failure population, and compared birth weights (BW) and NT-proBNP (brain natriuretic peptide) levels among different patient groups.
Methods: During 2012 and 2013 628 adult patients with different types of CMP were hospitalized in our center. Birth weight data were available for 130 patients; these patients were included in our observational study. The patients were categorized in groups according to the respective etiology of CMP: 49 patients had idiopathic CMP, 37 had ischemic CMP, 20 patients had secondary CMP (valvular, toxic or hypertensive), 14 patients had postmyocarditic CMP, 5 patients had hypertrophic CMP (HCM), and 5 patients had ARVD. The cut-off value for LBW was set at 2500g. We also recorded maximum NT-proBNP values.
Results: Average BWs among subgroups were as follows: postmyocarditic CMP 3135±743 g, ARVD 3414±250 g, ischaemic 3543±852 g, idiopathic CMP 3547±845 g, secondary CMP 3763±568 g, and HCM 3930±980 g. The lowest BW was found in postmyocarditic CMP and was shown to be significantly lower compared to the ischemic CMP group (p=0.05). Average NT-proBNP values (pg/ml) among subgroups were as follows: idiopathic CMP 5780±5734, postmyocarditic CMP 6216±3879, ischaemic CMP 3473±3708, secondary CMP 2695±2089, HCM 1719±1027, and ARVD 1487±2033. NT-proBNP was significantly higher in patients with idiopathic and postmyocarditic CMP, compared to ischaemic CMP (p=0.03 and p=0.02 respectively). Furthermore, in the group of patients with idiopathic CMP, the patients with LBW had significantly higher NT-proBNP values (102763±9227 pg/ml) than patients with normal birth weight (5245±5137 pg/ml; p=0.03). Considering all data, BW showed a weak but significant negative correlation to NT-proBNP values (Pearson correlation coefficient -0.17 (p=0.02)).
Conclusion: This observational study supports our previous findings of lower average BW among postmyocarditic CMP patients. An association was also established between LBW and NT-proBNP values in patients with idiopathic CMP. Additionally, birth weights were negatively correlated to NT-proBNP values. These data could potentially contribute to the fetal programming thesis, indicating that "in-utero" stress makes a lifelong influence on the CV system.

P6539 | BEDSIDE
Awake Cheyne-Stokes respiration: clinical and prognostic significance in a vast contemporary cohort of systolic heart failure patients

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Purpose: Cheyne-Stokes respiration characterized by periodic apnea/hyperpnea of central origin (CSR) has been described both during sleep and awake state in heart failure (HF) patients, and is associated with worse prognosis. However, comprehensive evaluation and prognostic value of awake CSR is still incomplete with contemporary medical and device therapy.
Methods: The study enrolled 439 consecutive HF patients (aged 65±13, 76% males; NYHA class I-II 67%, III-IV 33%, LVEF: 32±9%, mean±SD;) on optimal medical therapy. All patients underwent thorough clinical and neurohormonal evaluation, cardiorespiratory monitoring, cardiopulmonary exercise testing (CPET) and 24-hour continuous polygraphic recording of ECG and respiratory activity (nasal flow plus chest and abdomen respirograms) and were then followed-up (median 33 months; interquartile range 15-53), using cardiac mortality as endpoint.
Results: Three groups were identified according to severity of awake CSR (Apnea/Hypopnea Index, AHI<5,n=168, 38%; AHI 5-15, n=150, 34%; AHI>15, n=121, 28%). Higher degree of awake CSR was associated (p<0.01) with age, male gender, symptoms, higher LV end systolic diameter (but no differences in LVEF), higher plasma N-terminal fragment of probrain natriuretic peptide and norepinephrine, lower peak VO2, higher VE/VCO2, higher right ventricular dimension and pulmonary artery systolic pressure, higher frequency of non-sustained ventricular tachycardia. Sleep CSR was more frequent in patients with diurnal AHI>15, (median AHI: 35, interquartile range 26-46 vs. 6, i.r. 3-12 in patients with diurnal AHI<5 p<0.01). 53 events occurred at follow-up. At Kaplan-Meyer (KM) analysis, patients with AHI>15 had worse prognosis (Log Rank=6.5, vs diurnal AHI<5, p=0.01).
Conclusions: Awake CSR is associated with neurohormonal activation, worse right ventricular function increased arrhythmic burden, lower functional capacity and worst prognosis. Specific therapeutic strategies should be searched for diurnal CSR, which is a frequent finding in HF patients and harbors significant clinical informations and worse prognosis.

P6540 | BEDSIDE
CCR5del32 polymorphism is a protective factor in non-ischemic cardiomyopathy

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Objective: To gain insight into the long-term effect of the CCR5 genotype in patients with clinically suspected myocarditis or dilated cardiomyopathy (DCM). A 32-basepair deletion (del32) in the CC chemokine receptor 5 (CCR5, RANTES) gene leads to deficiency of this receptor for various chemokines. Homozygosity results in reduced susceptibility to HIV infections and is furthermore associated with an improved outcome in diabetes and coronary heart disease.
Methods: We determined its frequency by PCR in 300 consecutive patients (mean [±SD] age, 49.68±13.93 years; 194 men) with reliable information on the all cause six year mortality. Occurrence of the endpoint death was determined through direct contact with the patient, contact with family members or inquiries at the registration office. All patients gave written informed consent for genetic analysis. The protocol was approved by local medical ethics committee of the University Hospital.
Results: Fourteen out of 239 CCR5 wildtype individuals (group 1) had died within a 6-year period. In contrast, all group 2 patients with a CCR5del32 polymorphism (w/del32 (n=57) and del32/del32 (n=4)) were alive at the end of the study (Figure 1A). The reduced mortality of patients with a 32-basepair deletion (del32) (p=0.032) of the CCR5 receptor possibly indicates the CCR5del32 polymorphism as a protective factor in patients with acquired cardiomyopathies.
The CCR5 genotype did not correlate with a persisting myocardial inflammation. Diabetes was only present in wildtype patients but not in patients with impaired CCR5 receptor (0/46) (p=0.001) but the increased mortality rate was not associated with diabetes (p=0.182). DCM is frequently caused by myocardial infection and post-infectious inflammation in genetically predisposed patients and has a poor prognosis. In our cohort the frequency of cardiotropic viruses such as enteroviruses (EV), human herpesviruses 6 (HHV6) or erythroviruses (parvovirus

B19V) was not significantly different between group 1 and 2 (EV: 12.2%, vs 9.4%; (p=0.568), B19V: 33.3%, vs 18.7%, (p=0.076) or HHV6: 20.1% vs 15.1%, (p=0.408), respectively). Furthermore, there was no correlation between myocardial infection by enterovirus, HHV6 or erythrovirus with the 6-year-mortality (EV: p=0.514; HHV6: p=0.818; B19V: p=0.510, respectively).
Conclusion: Our data show, for the first time, that CCR5del32 polymorphism is an independent genetic factor that influences outcome in patients with clinically suspected myocarditis and DCM, not associated with myocardial inflammation, diabetes or viral infections.

P6541 | BEDSIDE
Daytime vs night-time central apnea in mild vs moderate-to-severe systolic heart failure

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Purpose: Central sleep apnea (CSA), characterized by periodic apnea/hyperpnea of central origin has been described both during night-time and day-time in systolic heart failure (HF) patients, and is associated with worse prognosis. However, its clinical significance in mild left ventricular dysfunction (left ventricular ejection fraction -LVEF- >40 <50%) has never been specifically addressed.
Methods: The study enrolled 439 consecutive HF patients (aged 65±13 years, 76% males; NYHA class I-II 67%, III-IV 33%, LVEF: 32±9%, mean±SD;) on guideline recommended therapy. Of these, 105 patients had mild left ventricular (LV) dysfunction (LVEF 40-50%, aged 68±12 years, 71% males; NYHA class I-II 67%, III-IV 33%, LVEF: 44±4%, N-terminal fragment of probrain natriuretic peptide -NT-proBNP- 786 ng/L, 225-2036) and 334 patients had moderate-severe LV dysfunction (LVEF<40%, aged 64±14 years, 77% males; NYHA class I-II 65%, III-IV 35%; LVEF: 28±8%; NT-proBNP 1486 ng/L, interquartile range 686-3399). All patients underwent thorough a 24-hour continuous polygraphic recording of ECG and respiratory activity (nasal flow, chest/ abdomen respirograms) and were followed up for cardiac events.
Results: Daytime CSA showed a similar prevalence in mild vs. severe LV dysfunction patients (apnea-hypopnea index, AHI>15, 23% vs 29%; AHI 5-15, 34% vs 34%; AHI <5: 43% vs 38%, p= NS). Night-time CSA was indeed less prevalent in mild vs severe LV dysfunction patients (apnea-hypopnea index, AHI>15, 52% vs 60%; AHI 5-15, 24% vs 24%; AHI<5: 24 vs 15%, p<0.05 for trend). Overall, 53 cardiac events occurred, 11 in mild LV dysfunction and 42 in moderate-severe LV dysfunction; median follow up was, respectively, 31months, i.r. 15-50 and 34 months, i.r. 15-54. In mild LV dysfunction, day-time CSA failed to predict prognosis while in moderate-severe LV dysfunction it identified patients who had worse prognosis (AHI>15 vs AHI<5, log-rank 6.6, p<0.05). Night-time CSA, on the other and, failed to show a prognostic value in both mild and moderate-severe LV dysfunction.
Conclusions: Central apnea is a frequent phenomenon even in patients with mild LV systolic dysfunction, where it could represent a compensatory and not yet detrimental factor; in fact, day-time CSA is similarly prevalent in the two subsets of the population (mild vs moderate-severe LV dysfunction) but it holds prognostic value only in more advanced disease states. Night-time CSA is more frequent in moderate-severe left ventricular dysfunction, but it lacks prognostic value in this population of guidelines-recommended therapy.

P6542 | BENCH
Increased circulating HMGB1 and decreased soluble TLR4 in myocarditis and dilated cardiomyopathy

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Purpose: Myocarditis is an inflammatory heart disease which can lead to the development of dilated cardiomyopathy and heart failure. Viral infection is a major cause of acute myocarditis. TLRs (Toll like receptors) are multi-ligand receptors playing an important role in inflammatory processes. Some TLRs have been reported to be responsible for the exacerbation of the inflammatory response to viral infection. In particular TLR4 and one of it's ligands HMGB1 (High Mobility Group Box 1 protein) appear to be involved in activation of the autoimmune response, which may lead to a chronic inflammatory response and to myocardial damage. Recently, some soluble forms of Toll like receptors comprising the extracellular receptor-domain and acting as ligand decoys have been described.
The aim of this study was to evaluate the HMGB1 and sTLR4 (soluble Toll like receptor 4) plasma levels in patients with viral myocarditis and dilated cardiomyopathy.
Methods: Observational clinical non-interventional study in patients with proven viral myocarditis (n=15; proof of viral infection by endomyocardial biopsy) and patients with dilated cardiomyopathy (n=15). Age-matched healthy volunteers served as controls (n=15). EDTA-plasma samples were analyzed for HMGB1 and sTLR4 by Western blotting and densitometric analysis. Cardiac ejection fraction was determined by echocardiography in the patient group.
Results: HMGB1 plasma levels were significantly increased in patients with myocarditis and to a similar extent in patients with dilated cardiomyopathy as compared to healthy controls (seven-fold increase). sTLR4 showed an opposite regulation with decreased levels in dilated cardiomyopathy (50% reduction) and even more so in myocarditis blood samples (75% reduction). Plasma levels of HMGB1 and sTLR4 showed a significant inverse correlation in myocarditis (r= - 0.71; p=0.007) and circulating plasma sTLR4 showed a positive significant correlation with cardiac ejection fraction as determined by echocardiography (r=0.69; p=0.02). Furthermore, co-immunoprecipitation demonstrated binding of HMGB1 by sTLR4-peptides.
Conclusions: Viral myocarditis is associated with increased plasma levels of circulating pro-inflammatory HMGB1 and decreased levels of soluble TLR4, leading to a pro-inflammatory imbalance which persists in dilated cardiomyopathy. The mechanisms modulating HMGB1 and sTLR4 plasma levels remain to be elucidated and might help to develop new therapeutic strategies for the management of viral myocarditis and prevention of dilated cardiomyopathy.

P6543 | BEDSIDE
Prevalence and severity of sleep apnoea syndromes in cardiac amyloidosis patients

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Background: Cardiac diseases are associated with a high prevalence of sleep apnoea syndrome (SAS), central or obstructive, particularly in heart failure. There is no data about prevalence and severity of sleep disordered breathing in cardiac amyloidosis patients, whether amyloidosis is systemic (AL), or transthyretin-related amyloidosis, senile (sTTR) or familial (fTTR).
Methods: Patients prospectively referred in our cardiology department between 2010 and 2013 for cardiac amyloidosis underwent clinical, biological, echocardiography and polygraphy assessment to diagnose sleep apnoea syndrome (SAS). The polygraph was recorded overnight in the cardiology ward using a computerized data acquisition system, which recorded oronasal airflow, chest and abdominal effort, pulse oximetry, snoring, actimetry and body position. SAS was defined as an apnoea-hypopnoea index greater or equal to 5 events/h.
Results: Sixty-three patients were included, of whom 28 had AL, 20 fTTR and 15 sTTR. Mean (SD) age, left ventricular ejection fraction, and body mass index of the overall cohort were respectively 70±13 years, 49±14% and 25±4 kg/m^2. The prevalence of SAS was 88%. Prevalence of SAS was respectively 86%, 95%, and 86% in AL, fTTR and sTTR (p>0.05). 31% of syndromes were classified as central (CSA) and 69% as obstructive (OSA). The mean apnoea hypopnoea index was 20±15 events/h and was superior to 15 events/h (that should be treated by nocturnal ventilation) in 35 (56%) patients of the total cohort, and respectively 13 (21%), 11 (17%) and 11 (17%) patients in AL, fTTR and sTTR (p>0.05).
Conclusion: The prevalence of sleep-disordered breathing is high (88%) in cardiac amyloidosis population, with most syndromes having an obstructive pattern. Effect of SAS treatment should be investigated in this population.

P6544 | BEDSIDE
Total isovolumic time correlates with limited exercise capacity in HFpEF – its shortening with stress suggests significant rise of filling pressure

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Background and aim: Patients with heart failure (HF) and preserved left ventricular (LV) ejection fraction (EF) (HFpEF) due to systemic hypertension (SHT) are limited by exertional symptoms. The exact underlying cardiac dysfunction for this scenario is not completely understood. We aimed in this study to examine objectively the exercise capacity in a group of such patients and determine its potential relationship to other functional disturbances, which may explain disease pathophysiology.
Methods: Fifteen patients with HFpEF due to SHT (mean age 70±8 years) but no valve disease and 14 healthy individuals (age of 65±10 years) underwent resting and peak exercise echocardiography using conventional protocol, tissue Doppler and speckle tracking techniques. LV total isovolumic time (t-IVT) and Tei index, which indirectly reflect the global cavity dyssynchrony were also measured. The differences between resting and peak exercise values were determined (Δ). Exercise capacity was calculated as the workload (Watt) divided by body surface area (BSA).
Results: Patients had lower Watt/BSA compared to controls (p<0.001). LVEF increased during exercise in normals (mean Δ EF = 10±8%) but failed to do so in patients (mean Δ EF = 0.9±8%, p<0.001 between groups). T-IVT that was longer in patients compared to controls (8.9±2 vs. 6.6±2 s/min, p=0.004), shortened with exercise opposite to controls (Δ 4.3±2 vs. 1.2±2.2 s/min, p=0.001). Tei index also decreased at peak exercise (Δ 0.26±0.14 vs. 0.04±0.17, p=0.001). Δ t-IVT, but not Tei index, also correlated with Watt/BSA (r=-0.53, p=0.003).
Conclusion: HFpEF patients with hypertensive LV disease have significantly limited exercise capacity which, with attenuated EF, but was related to the severity of global dyssynchrony. Shortening of t-IVT with exercise is likely to be on the expense of raised filling pressures and hence causing symptoms.

BIOMARKER UPDATE

P6546 | BEDSIDE
Which heart failure patients profit from natriuretic peptide guided therapy? A meta-analysis from individual patient data of randomised trials

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Background: Previous analyses suggest that heart failure (HF) therapy guided by B-type natriuretic peptide (BNP) or NT-proBNP might not be equally effective in all HF patients, particularly those aged >75 years, but reasons remain unclear.
Methods: To determine interactions between (NT-pro)BNP-guided therapy and reduced (HFrEF, n=1731) versus preserved ejection fraction (HFpEF, n=301) as well as comorbidities (hypertension, renal failure, COPD, diabetes, cerebrovascular insult [CVI], peripheral vascular disease [PVD]) on outcome, individual patient data (n=2137) from 8 (NT-pro)BNP guidance trials were analysed: BATTLESCARRED (n=242), Vienna study (n=188), PRIMA (n=345), PROTECT (n=151), SignalHF (n=252), TIME-CHF (n=622), Christchurch study (n=69), UPSTEP (n=268); all were NT-proBNP-guided with the exception of UPSTEP. Endpoints were all-cause mortality and HF admission.
Results: Whereas in HFrEF patients (NT-pro)BNP guided compared to symptom-guided therapy resulted in lower mortality (HR=0.78, p=0.03) and less HF admissions (HR=0.80, p=0.02), no such effect was seen in HFpEF (mortality: HR=1.22, p=0.41; HF admissions HR=1.01, p=0.97). The interaction between group allocation and EF was significant for both endpoints (p=0.02 mortality; p=0.007 HF admission), which remained present after adjustment to differences in patient characteristics (age, gender, BMI, co-morbidities, NT-proBNP levels). Mortality (HR=1.15, p=0.28) and HF admissions (HR=1.20, p=0.12) in HFpEF patients did not differ significantly from those with HFrEF.
Age (mean 74±11 years) interacted with treatment allocation independently of EF regarding mortality (p=0.02), but not HF admission (p=0.54). However in patients of both EF groups, this interaction with age regarding mortality was fully explained by interaction of treatment allocation and co-morbidities and was absent after inclusion of these interactions into equation. In HFpEF patients, presence of renal failure provided strongest interaction (p<0.01), whereas in HFrEF patients, the presence of at least two of the following co-morbidities provided strongest interaction (p<0.01; COPD, diabetes, CVI, PVD). Effects of (NT-pro)BNP guided therapy were more substantial in patients with history of hypertension (interaction p=0.02 in HFpEF, p=0.20 in HFrEF).
Conclusion: The benefits of therapy guided by (NT-pro)BNP were only present in HFrEF but not in HFpEF patients. Consistent with HF care in general, co-morbidities strongly influence the response to (NT-pro)BNP guided therapy and explain the perceived lower efficacy of this approach in elderly patients.

P6547 | BENCH
RNA sequencing analysis reveals new data of the atrial natriuretic peptide origin in patients with dilated and ischemic cardiomyopathy

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Purpose: The atrium is the major site of ANP synthesis, which has been said to increase in heart failure as a result of increased production in the left ventricular (LV) myocardium. This is a key issue related to its diagnostic and prognostic capabilities. We aimed to evaluate protein levels of proANP and ANP and the enzymes that cleave the natriuretic peptides, corin and furin, in the LV tissue of heart transplant patients with dilated (DCM) and ischemic (ICM) cardiomyopathy compared with control donors (CNT). We also evaluate mRNA levels of ANP gene (NPPA) by RNA sequencing in the same tissue.
Methods: Seventy-three LV tissue samples from ICM (n=30) and DCM (n=33) patients and CNT (n=10) were analyzed by Western blot and RNA sequencing.
Results: Comparing protein levels according to etiology, neither DCM nor ICM showed levels of proANP or ANP different from those of CNT. However, NPPA was increased in both groups compared to CNT (DCM 32 fold, p<0.0001; ICM 10 fold, p<0.0001). Corin (but not furin) was elevated in the ICM group compared to CNT (112±24 vs. 100±7, p<0.05), and its level was inversely related with LV ejection fraction (LVEF) (r=-0.399, p<0.05).
Conclusions: Patients present elevated levels of NPPA but not of proANP or ANP proteins in LV tissue, which may be due to posttranscripcional regulation of NPPA or different secretion ways of ANP between the atrium and ventricle. Moreover, there are differences between DCM and ICM in corin levels, indicating that a different molecular mechanism may exist that converge in this syndrome. Further, LV concentration of corin is inversely related to LVEF in ICM.

P6548 | BEDSIDE
A novel troponin T peptide in acute breathless patients presenting to ED

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Purpose: We have recently identified a novel circulating peptide derived from the 5'-upstream open frame region of the cardiac Troponin T gene (TnTuORF) and reported its potential use in patients with acute coronary syndromes (ACS). Here, we report its potential use in patients presenting to a single center hospital ED with the primary complaint of acute breathlessness.
Methods: 352 patients with the primary complaint of breathlessness, not resulting from trauma, were prospectively recruited upon presentation to the Emergency Department of our Hospital. Adjudicated diagnoses were made by two cardiologists with access to all test results available from the hospital stay including echocardiography, computed tomography (CT) scan, ventilation perfusion lung scan, pulmonary function, and inpatient laboratory tests. Patient events were followed for 30 and 90 days post-index admission. Blood samples were drawn at presentation, +24 hours and at hospital discharge for the measurement of hsTnT (Roche), TnI, NT-proBNP and TnTuORF (in-house research assay). The diagnostic and prognostic utility of TnTuORF alone and in combination with other markers was assessed by ROC AUC analysis. Statistical correlations were determined using Spearman's rank order. P<0.05 was considered significant.
Results: 138 patients (39%) had acute decompensated heart failure (ADHF), 50 (14%) had acute MI and 112 (32%) had exacerbation of asthma or COPD. Presentation TnTuORF had significant negative correlations with presentation NT-proBNP (r=-0.184, P<0.01), hsTnT (r=-0.130, P<0.05) and plasma creatinine (r=-0.127, P<0.05). Presentation TnTuORF alone did not diagnose ADHF or MI and did not add to NT-proBNP diagnosis of ADHF. TnTuORF had the ability to diagnose asthma/COPD (ROC AUC = 0.63, P<0.01) but the ratio of TnTuORF/NT-proBNP gave the best AUC for the diagnosis of asthma/COPD (AUC = 0.74, P<0.001). The ratio of TnTuORF/NT-proBNP also predicted inpatient return with COPD at 30 (AUC = 0.64, P<0.05, n=25) and 90 days (AUC = 0.62, P<0.01, n=47). Finally, the ratio of total cardiac troponin over TnTuORF ([hsTnT*TnI]/TnTuORF, TroponinPLUS) improved the AUC of hsTnT for the diagnosis of acute MI from 0.77 to 0.81 (P<0.05) and could predict inpatient heart failure within 30 days (AUC = 0.87, P<0.01, n=7) and 90 days (AUC = 0.74, P<0.01, n=17).
Conclusions: This data suggests, alongside its potential in chest pain patients, TnTuORF may have diagnostic or prognostic use in assisting NT-proBNP/hsTnT discrimination of ADHF/MI in acute breathless populations, especially those with complicating COPD/asthma.

P6549 | BEDSIDE
Changes of natriuretic peptides predict hospital admissions in patients with chronic heart failure. A meta-analysis

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Purpose: The relationship between B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasma levels and risk of cardiovascular events in patients with chronic heart failure (HF) has been previously demonstrated.
However, it is unclear whether changes of BNP and NT-proBNP predict morbidity in chronic HF patients. The aim of our study was to explore the association between changes in BNP and NT-proBNP plasma levels and risk of hospital admission for HF worsening in chronic HF patients.
Methods: The MEDLINE, Cochrane, ISI Web of Science and SCOPUS databases were searched for articles about HF treatment until August 2013. Randomized trials enrolling patients with systolic HF, assessing BNP and/or NT-proBNP at baseline and at end of follow-up and reporting hospitalization for HF were included in the analysis. Meta-regression analysis was performed to test the relationship between BNP and NT-proBNP changes and clinical end-point. Sensitivity analysis was performed to assess the influence of baseline variables on results. Egger's linear regression was used to assess publication bias.
Results: Nineteen trials enrolling 12,891 participants were included. The median follow-up was 9.5 months (interquartile range 6-18) and 22% of patients were women. Active treatments significantly reduced the risk of hospitalization for HF worsening (Odds Ratio: 0.678; 95% Confidence Interval [CI]: 0.547 to 0.841; p=0.000). In meta-regression analysis, changes in natriuretic peptide levels (both BNP and NT-proBNP) were significantly associated to risk of HF hospitalization after the removal of significant heterogeneity (Regression Coefficient [RC]: 0.036; 95% CI: 0.015 to 0.056; p=0.002). Additionally, when changes in BNP and NT-proBNP were separately assessed, they were both were significantly associated with risk of hospitalization for HF worsening, even after removal of significant heterogeneity (BNP - RC: 0.037; 95% CI: 0.003 to 0.070; regression p=0.038. NT-proBNP - RC: 0.029; 95% CI: 0.001 to 0.568; regression p=0.046). Results were confirmed by sensitivity analysis. No publication bias was detected.

Conclusions: In HF patients, reduction of BNP or NT-proBNP levels is associated with reduced risk of hospitalization for HF worsening.

P6550 | BENCH
Dipyridamole-induced C-type natriuretic peptide mRNA overexpression in minipig with pacing-induced left ventricular dysfunction

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Purpose: Molecular, neurohormonal, and haemodynamic changes occur in the setting of left ventricular dysfunction (LVD) of ischemic or non-ischemic origin. Recently it was demonstrated that dipyridamole (DP), a phosphodiesterase inhibitor able to increase the intracellular levels of cAMP and cGMP, restores ischaemic tissue blood flow stimulating angiogenesis through a protein kinase A-dependent eNOS pathway. C-type natriuretic peptide (CNP), a potent regulator of vascular tone, is expected to mimic the migration-stimulatory effect of NO via a cGMP dependent mechanism. Aim of this study was to assess the role of concomitant treatment with DP on CNP levels in blood and myocardial tissue of minipigs with pacing-induced LVD.
Methods: LVD was induced by pacing at 200 bpm in the right ventricular (RV) apex of minipigs undergoing concomitant DP therapy (5 mg/kg p.o.) (DP+, n=4) or placebo (DP-, n=4). Four sham operated minipigs (C-SHAM) were used as controls. All animals underwent a 2D EchoDoppler examination immediately after single chamber pace-maker implantation and after 4-weeks of RV tachycardic pacing. Animals were sacrificed after 4 weeks pacing and cardiac tissue collected in each minipig from 6 regions of the LV wall. In LVD animals blood samples were also drawn at baseline and after 4 weeks pacing and CNP plasma levels were determined by radioimmunoassay. CNP, natriuretic peptide receptor (NPR)-B, NPR-C and BNP cardiac mRNA expression were evaluated by Real Time-PCR in all animals.
Results: After 4 weeks of pacing, LV fractional shortening (LVFS) was markedly reduced in DP- and to a lower extent in DP+ (DP-:21.5±2%, DP+:31.4±4%) as compared to baseline (DP-:38.0±3%, DP+:40.3±1.4%, $p<0.0001$, p=0.03 respectively). LVFS was unchanged in C-SHAM (43±3% vs 44±2%). CNP gene expression resulted lower in DP- (0.13±0.03) with respect to C-SHAM (0.51±0.1) and DP+ (0.43±0.2) as well as NPR-B (C-SHAM: 0.42±0.06, DP-:0.32±0.06, DP+:0.63±0.1) (p=0.011 DP- vs DP+). NPR-C mRNA expression was significantly ($p<0.001$) lower both in DP-(0.33±0.06) and DP+ (0.45±0.07) with respect to C-SHAM (1.2±0.2). As expected, the mRNA expression BNP levels were higher in LVD as compared to C-SHAM. CNP plasma levels resulted higher in DP+ compared to DP- (22.0±7.1, 15.8±3.8 pg/ml, respectively, p=0.37).
Conclusion: These data suggest that DP may serve as a preconditioning agent to increase the protective CNP-mediated endocrine response in LVD. This response, mediated by its specific receptor NPR-B, may open new insights on molecular targets for treatment of LVD.

P6551 | BENCH
Dual-acting angiotensin-receptor neprilysin-inhibition attenuates post-myocardial infarction cardiac remodelling and angiotensin-II-induced cardiorenal injury in vitro

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Background: Novel angiotensin-receptor neprilysin (NEP) inhibitors (ARNi) demonstrated benefits above single RAAS-blockade in early clinical trials, but mechanisms underlying cardiorenal protection by ARNi are unknown. We evaluated ARNi in cardiac remodelling after experimental myocardial infarction (MI), and in angiotensin-II (AngII) induced hypertrophy and fibrosis in cardiorenal cell lines.
Methods: One week after induction of MI, adult male rats were randomized and treated for four weeks with the ARNi LCZ696 (68 mg/kg body weight PO; ARNi-MI, n=11) or vehicle (VHC-MI, n=6). Echocardiography and organ weights served to assess cardiac structure and function at 5 weeks after MI. AngII-stimulated (100nM) 3[H]leucine-incorporation in cardiomyocyte over 60 h served to evaluate cardiac hypertrophy. 3[H]proline-incorporation in cardiac fibroblast or renal mesangial cells over 48 h (CF) served to evaluate collagen accumulation. Cells were pre-incubated with valsartan (VAL), NEP inhibitor LBQ657 (LBQ; 10μM), or both (ARNi).
Results: MI-ARNi had lower heart weights (1168±35 vs 1319±21 mg) and left ventricluar (LV) end-diastolic diameter (9.7±0.2 vs 10.5±0.3), and higher LV ejection fraction (60±2 vs 47±5%) compared to MI-VHC (all $p<0.05$). Cell data, see table: ARNi at high dose abrogated AngII-stimulated cellular cardiac hypertrophy and cardiorenal fibrosis.

Effects of ARNi in vitro

VAL (mM)	0.0	0.03	0.1	1.0
Cardiomyocytes: hypertrophy				
VAL alone	128±2****	116±1##	111±2###	109±3###
ARNi (VAL+ LBQ 1μM)	109±2###	107±3###	110±3###	98±3###
Cardiac fibroblasts: collagen accumulation				
VAL alone	211±6****	164±6###	144±5###	113±3###
ARNi (VAL+ LBQ 1μM)	170±11###	123±7###	115±4###	101±3###
Renal mesangial cells: collagen accumulation				
VAL alone	144±6****	114±5###	111±6###	–
ARNi (VAL+ LBQ 1μM)	118±4###	103±7###	97±13###	–

Cell data normalized to unstimulated control (=100%). ****$p<0.0001$ vs unstimulated control, ###$p<0.001$ vs stimulated control.

Conclusions: ARNi attenuates cardiac remodelling after MI, possibly by potent anti-fibrotic and anti-hypertrophic effects in cardiorenal tissues.

P6552 | BENCH
Exogenous administration of Interleukin-18 suppresses cardiomyocyte hypertrophy and mortality but not contractile function in pressure overloaded IL-18 null mice

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Background: We previously reported that circulatory Interleukin-18 (IL-18) level elevates according to severity of heart failure (HF) patients. However, the roles of circulatory IL-18 in Chronic HF have not been fully elucidated. Continuous infusion of IL-18 induces pathological cardiac hypertrophy and fibrosis, whereas IL-18 null mice were fragile to pressure overload. We hypothesized that systemic (circulatory) and local (cardiac) IL-18 have distinct effects on HF and cardiac remodeling.
Purpose: The purpose of this study was to elucidate the role of circulatory IL-18 in adaptation to pressure overload in IL-18 null mice.
Methods: Ten-week-old male C57BL6/J-background wild type (WT) mice and IL-18 null (IL-18–/–) were subjected to transaortic constriction (TAC). Sequential serum IL-18 levels myocardial IL-18 mRNA expressions were determined by ELISA and qRT-PCR in WT mice. From 1 week before TAC surgery, IL-18 null mice were administered either (IP) saline intraperitoneally or recombinant IL-18 intraperitoneally (10ng every other day) for 3 weeks. Cardiac function was assessed by transthoracic echocardiography. Two weeks after TAC operation, myocardial samples were obtained. Haematoxylin and eosin stained sections and Masson's trichrome staining sections were prepared.
Results: IL-18 concentration in serum and IL-18 expression in myocardial tissue increased gradually after TAC in WT mice. Forty-seven % of TAC-operated IL-18–/– mice and 12% of TAC-operated WT mice died of heart failure by 14days. TAC-operated IL-18–/– mice exhibited more severe left ventricular (LV) remodeling, characterized by reduced LV fractional shortening (34±2% vs. 46±1%, $p<0.05$), cardiomyocyte hypertrophy, extensive interstitial fibrosis and elevation of fetal gene expressions (α-skeltal actin: 20.9±2.0 folds vs. 6.5±1.3 folds, $p<0.05$) compared with TAC-WT mice. Recombinant IL-18 given intraperitoneally improved the survival rate to 100% following TAC operation in IL-18–/– mice. Furthermore, exogenous IL-18 administration suppressed ventricular fetal gene expressions to non-TAC-operated level, whereas LV enlargement and contractile dysfunction were only partially suppressed in IL-18–/– mice following TAC (LV fractional shortening: 39±2%).
Conclusions: Circulatory IL-18 exerts opposing effects on cardiomyocyte hypertrophy and cardiac fibrosis under pressure-overload. IL-18 produced in the heart may have an effect such as preserving contractile function.

P6553 | BEDSIDE
Renal sympathetic nerve activity in heart failure is accelerated and correlated with cardiac sympathetic nerve activity evaluated by 123I-MIBG Imaging

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Background: Cardiac sympathetic nerve activity evaluated by cardiac 123I-MIBG scintigraphy has been shown to have diagnostic and prognostic significance in heart failure (HF). Renal sympathetic nerve activity also is accelerated in some type of hypertension. However, it remains unknown whether there is correlation between heart and kidney about sympathetic nerve activity (SNA) in heart failure. In this study, we evaluated SNA of heart and kidney in HF by 123I-MIBG Imaging.
Methods: The subjects were 101 consecutive patients hospitalized for HF (NYHA class III and IV) and 30 consecutive patients served as a control group without HF (group C) between March2012 and December2013. HF Patients were classified into 2 groups: group R (LVEF<50%: mean 35.2+8.3%, n=53, 69.9+12.6 years) and group P (LVEF>50%: mean 65.3+6.1%, n=48, 76.3+12.1 years). Group C had normal LV function (mean LVEF 67.1+4.6%, n=30, 49.2+13.0 years). 123I-MIBG scintigraphy was evaluated as the heart-to-mediastinum ratio and the kidney-to-mediastinum ratio in the delayed image (H/M and K/M) and the washout rate (heat: hWoR and kidney: kWoR) respectively. Plasma BNP concentration, BUN,Cr and eGFR were also determined in each subject with HF.
Results: In group R & P, H/M was significantly lower and hWoR was significantly higher than that in group C (H/M (R2.04±0.54*, P2.21±0.58*, C2.95±0.44), hWoR (R55.6±9.7*, P48.2±13.6*, C27.7±10.7%: *$p<0.01$ vs. C). Although BNP

was higher in group R than P (R780±589**, P417±586 pg/ml, **p<0.01 vs. P), there is no significant differences in H/M and eGFR between groups R and P [eGFR (R: 58.7±20.3, P: 52.4±17.5 ml/min/1.73m^2)]. Correlation between heart and kidney in HF was significant [Y=0.976+0.357X: r=0.43, p<0.00 1 (K/M and H/M) and Y=63.99+0.253X: r=0.29, p<0.01 (kWoR and hWoR)]. Correlation between heart and kidney in group R and P also was significant respectively [R: r=0.39, p<0.01, P: r=0.45, p<0.01 (K/M and H/M)].
Conclusions: These results suggest that there is a positive correlation between heart and kidney about SNA in HF. Furthermore, Renal SNA is correlated with cardiac SNA regardless of type of heart failure.

P6554 | BEDSIDE
Prognostic value of soluble ST2 in patients with dyspnea

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Objectives: Soluble ST2 (ST2) has emerged as a novel biomarker with exceptional predictive value in heart failure. The aim of this study was to investigate prognostic utility of ST2.
Methods: We recruited 138 patients presenting to the emergency department and the outpatient department with dyspnea. We performed to measure ST2 level and BNP. Outcome measure were all-cause mortality and readmission at 6 month. The prognostic value of ST2 was evaluated in comparison to BNP.
Results: Median concentrations of ST2 were higher among decedents and patients with readmission at 6 month (110.088 vs. 66.756 ng/ml; p=0.0035). Median concentrations of BNP were also higher among decedents and patients with readmission at 6 month (500.00 vs. 274.477 pg/ml; p=0.0497). Applying receiver operating characteristic (ROC) analysis, the area under the curve (AUC) for ST2 and BNP to predict 6-month mortality and readmission were 0.750 and 0.652, respectively. In this study, ST2 was more specific predictor compared with BNP.
Conclusion: ST2 is a strong and independent predictor of 6-month mortality and readmission. ST2 may provide clinicians with an additional tool for guiding treatment in patients with dyspnea.

P6555 | BEDSIDE
Sustained hyponatremia in acute phase associates with high in-hospital mortality in acute heart failure syndrome patients

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Background: Hyponatremia is one of the most common electrolyte disorders in acute heart failure (AHFS) patients. Many studies have shown that presence of hyponatremia at admission associate with high morbidity and mortality in AHFS patients. However, in some patients with AHFS, hyponatremia will be corrected by general treatment for AHFS. In this study, we investigated whether correction of hyponatremia in acute treatment for AHFS associates to prognosis.
Methods: We retrospectively included 554 AHFS patients who were admitted to two hospitals during January 2011 to December 2012. Patients were divided into three groups; hyponatremia at admission and also at 2 days after admission (hypo-hypo group), hyponatremia at admission and not at 2 days after admission (hypo-normo group), and normonatremia at admission (normo group). Hyponatremia was defined as serum sodium concentration ≤135 mmol/L. Endpoint was in-hospital mortality.
Results: Of all cohorts, 42 patients (7.6%) were in hypo-hypo group, 40 patients (7.2%) were in hypo-normo group, and 472 patients (85.2%) were in normo group. In-hospital mortality for these three-groups were 21.4%, 12.5%, and 5.9%, respectively (P=0.005). In multivariate analysis, hypo-hypo group was an independent predictor for in-hospital mortality (HR 2.74, 95% CI: 1.11-6.78, P=0.029) but hypo-normo group were not (HR 1.78, 95% CI: 0.60-5.29, P=0.30).
Conclusion: In AHFS patients, sustained hyponatremia of more than 2 days after admission contributes to worse prognosis.

P6556 | BEDSIDE
Impact of left ventricular hypertrophy and plasma norepinephrine level for cardiovascular events in elderly hypertensive patients - JMS ABPM wave 1 study

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Background: The predictive value of electrocardiographic left ventricular hypertrophy (LVH) for cardiovascular disease (CVD) onsets has been well established. However, the underlying mechanism remained unclear.
Methods and results: 514 hypertensive patients (mean 72.3 years old; 37% men) were recruited. LVH was defined as Sokolow-Lyon voltage over 35mV. The incidence of CVD was prospectively ascertained. During an average of 41 month (1751 person-years), there were 43 stroke and 3 myocardial infarction. At baseline, compared with patients without LVH, those with LVH had higher levels of 24-hour blood pressure (mean 135.7/77.2 mmHg vs 148.8/83.8 mmHg) and circulating norepinephrine (geometric mean 336.3 pg/ml vs 404.6 pg/ml) even after adjusted for some covariates (all p<0.01); whereas circulating levels hemostatic factors (i.e. plasma fibrinogen, plasminogen activator inhibitor-1, prothrombin fragment 1+2), glucose and lipid parameters and plasma renin activity were not different between two groups (p=NS). A multivariable analysis showed that hazard ratio for CVD in the presence of LVH was 2.9 and highest quartile of norepinephrine (≥538 pg/ml, n=128) was 1.9 (both p<0.05); there was an additive effect of LVH and high norepinephrine level on CVD risk.
Conclusions: In older hypertensive patients, LVH is associated with high 24-hour BP and high norepinephrine level. However the predictive value of LVH is independent of 24-hour BP and circulating norepinephrine level.

P6557 | BEDSIDE
Cardio-renal syndrome revealed increased neurohormonal activity, tubular and myocardial damage respect to heart failure patients with preserved renal function

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Purpose: Cardio renal syndrome (CRS) is associated with increased cardiovascular morbidity and mortality, however its neurohormonal and biomarker pattern has been poorly evaluated.The aim of the study was to measure inflammatory activation, neurohormonal status and kidney and myocardial damage in patients with CRS compared to patients with Heart Failure (HF) and preserved renal function.
Methods: we analyzed 246 patients on the basis of renal function (Group I 120 patients with preserved renal function defined as eGFR>50 ml/min/1,73 m^2, and Group II 126 patients with eGFR<50 ml/min/1,73 m^2). In each group Interleukin-6 (IL6), Tumor necrosis factor (TNFα) B-type natriuretic petide (BNP), Neutrophil Gelatinase-Associated Lipocalin (NGAL), Troponin T (TnT), osteoprotegerin (OPG) and blood urea nitrogen (BUN) were measured. The power of all laboratory parameters in detecting CRS was evaluated by Receiver Operating Characteristics (ROC) curve analysis and logistic regression analysis.
Results: A significant increase in BNP in CRS patients compared to HF patients with preserved renal function, (626.4 pg/mL IC 518-749 vs 487.8 pg/mL IC 411-578 p<0,05) was revealed. IL-6 was significantly higher in CRS group (9.58 pg/mL IC 7-13 vs 5.93 pg/mL IC 3.9-8.8 p<0.05). NGAL measurements revealed more increased levels in CRS respect to HF group (156 ng/mL IC 129-186 vs 89,1 ng/mL IC 72-109 p<0.0001). TnT was increased in CRS group respect to HF group (0.62 [0.51-0.75] vs 0.21 [0.15-0.28] mg/L p<0.001). TNFα and OPG were similar in both groups. Patients with CRS showed increased levels of Urea (BUN) and urea /creatinine ratio (108.9 mg/dL IC 98-120 vs 51 mg/dL IC 46-55 p<0,0001; 86 IC 75-96 vs 43 IC 37-48 p<0,0001 respectively). However, the ROC curve analysis showed that only NGAL levels >113,5 ng/ml, BUN >78 mg/dL, BUN creatinine ratio>46,3 and TnT >0.27 mg/mL can discriminate patients with cardio-renal syndrome from patients with HF and preserved renal function, with good sensitivity and specificity (p<0,01).
Conclusions: in patients with CRS renal tubular damage is increased respect to patients with HF and preserved renal function. These patients also displayed higher neurohormonal and cardiac injury activation. The current biomarkers pattern could be used for an early diagnosis of renal impairment in acute and chronic HF.

DIASTOLIC DYSFUNCTION I

P6559 | BEDSIDE
Collapsibility of inferior vena cava as a predictor of renal dysfunction and clinical outcomes

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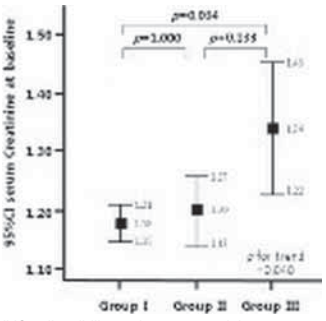
Background: Renal dysfunction is frequently observed in patients with heart failure with preserved left ventricular ejection fraction (LVEF) and renal vein congestion may be a cause of renal dysfunction. However, there are few studies that investigated this hypothesis. Collapsibility of inferior vena cava (IVC) during inspiration is a surrogate of estimated right atrial pressure and we investigated whether IVC collapsibility can predicts worse clinical outcomes.
Methods: We reviewed echocardiograms and measured maximum/minimum diameter of IVC and IVC collapsibility from the past medical database in our institute. Baseline clinical information and blood chemistry was obtained as well. Clinical status was assessed during follow-up.
Results: There were 1,166 patients enrolled in the study (Mean age = 63.8±13.4 years, 676 male). 929 patients had good collapsibility of IVC (≥50%, group I), 171 had partial collapsibility (≥25 and <50%, group II), while 61 patients had poor collapsibility (<25%, group III). After adjustment for age, sex, body mass index, LVEF, LV mass index, diabetes mellitus and heart failure, group III had significantly higher concentration of serum creatinine (sCr) as compared with group I (1.34±0.06 [95%CI, 1.22-1.46] mg/dl vs. 1.18±0.02 [95%CI, 1.15-1.21] mg/dl, p=0.034) at baseline. During follow-up (duration=1982±468 days), 67 patients died and group III independently predicted mortality after multivariate adjustment (p=0.008, OR=2.658).



IVC collapsibility and serum creatinine.

Conclusions: Patients with poor IVC collapsibility had worse renal function and higher mortality rate than those with good IVC collapsibility. Our investigation suggested systemic venous congestion aggravates renal dysfunction and independently predicts mortality.

P6560 | BEDSIDE
Electro-mechanical alterations in patients with long QT syndrome

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Purpose: Long QT syndrome (LQTS) is an arrhythmogenic cardiac ion channelopathy which has been considered a purely electrical disease. However, recent reports have indicated mechanical abnormalities in LQTS patients. We aimed to explore systolic and diastolic function in LQTS patients.
Methods: We included 192 genotyped LQTS patients with no concomitant cardiac disease. Age and sex matched healthy individuals served as controls (n=59). By echocardiography, we assessed left ventricular (LV) ejection fraction (EF) and speckle tracking global longitudinal strain (GLS) (16 LV segments). E-wave, A-wave, E deceleration time and e' (mean of septal and lateral e') were recorded by Doppler. Left atrial volume index (LAVI) was calculated. Heart rate corrected QT interval (QTc) was assessed by 12-lead ECG.
Results: In the 192 LQTS subjects, systolic function by GLS and diastolic function by e' and E deceleration time were reduced compared to healthy (all $p<0.05$) (Table). LAVI was enlarged in LQTS ($p<0.01$). QTc and LAVI correlated in LQTS ($R=0.17$, $p<0.05$), but not in healthy ($R=0.33$, $p=0.13$).

Findings in LQTS and healthy individuals

	Healthy control (N=59)	LQTS mutation positive (N=192)	p-value
Age	37±10	36±16	0.43
Female (n (%))	31 (53)	117 (61)	0.25
Heart rate	66±10	64±12	0.09
QTc (ms)	391±26	467±40	<0.01
EF (%)	61±5	61±5	0.74
GLS (%)	–22.5±1.9	–21.6±2.0	<0.01
e' (cm/s)	12.2±2.2	10.4±2.7	<0.01
E deceleration time (ms)	158±28	187±41	<0.01
E/A	1.9±0.6	1.7±0.7	0.07
E/e'	6.4±1.7	7.2±2.2	0.06
LAVI (ml/m^2)	26±5	30±8	<0.01

Conclusion: LQTS patients had a subtle reduction in both systolic and diastolic function compared to healthy. LAVI was enlarged in LQTS, indicating longstanding diastolic alterations. Furthermore, prolonged QTc was related to increased LAVI in LQTS, indicating an electro-mechanical association. These alterations may represent mechanical consequences of ion channel disease.

P6561 | BENCH
Cardiopulmonary exercise testing in diastolic heart failure: the link that has been missing

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Background: Dyspnea is a common consequence of hypertension even in pts with preserved left ventricular systolic (LVSF) and diastolic function (DVSF). Cardiopulmonary exercise testing (CPET) has been validated in the stratification of patients with diastolic heart failure (DHF), and its combination with stress echo showed a great potential in unmasking DHF. However, the relationship between CPET and stress echo parameters still remained undetermined.
Objective: To analyse the parameters of combined stress echo CPET in patients with hypertension, exertional dispnea with normal resting LVSF and LVDF in the early detection of DHF.
Methodology: We examined 82 pts with hypertension, exertional dyspnea and normal restng LVSF and LVDF. All pts performed combined stress echo CPET (supine bycicle, ramp protocol, 15W/min increments). Standard M-mode and 2-D echo measurements at rest, continuous echo monitoring (to exclude myocardial ischemia) and DF assessment at the top of the exercise, have been performed. We measured transmitral flow with pulsed doppler, and annular mitral velocities (e' and a' using TDI) according to guidelines using E / e ' as a main echo determinant DF. We excluded patients ≥65 years old in order to decrease the influence of age on LV diastolic properties.
Results: DHF (E/e' ≥15) was found in 7/82 pts (8.5%) during combined CPET stress echo test. There was no significant difference in LV EF in pts with and without DHF. Patients with DHF had lower peak VO2 (14.8±2.2 vs 20.3±5.5 ml/kg/min; p=0.021), and VO2 at the VAT (p=0.035), lower O2 pulse (p=0.04) and impaired ventilatory response with higher VE/VCO2 slope (p=0.033), and lower ΔpetCO2 (p=0.021). However there was no statisticaly significant difference in double product and circulatory power in pts with and without DHF. Multivariant analysis showed that VE/VCO2 slope was an independant predictor of DHF (p=0.033; RR 25; 95%CI: 1.3 -504.0). There was a strong correlation between VE/VCO2 slope and E/e' (r=0.69; p=0.0001). Value of VE/VCO2 best predictive for DHF in this group of pts according to ROC curve was 32.9 (Sn 100%, Sp 91%)
Conclusion: Combined stress echo CPET has very high accuracy to detect DHF in its early phase in the presence of normal resting echo values. The exercise test unmasked impaired ventilatory response in patients with dyspnea with excellent correlatiion between VE/VCO2 slope and E/e' relationship confirming the need for assessment the diastolic propertis during the effort even in patients with normal resting LV function

P6562 | BENCH
Long-term therapy with Bendavia (MTP-131) reverses myocardial structural and molecular abnormalities in a pig model of hypertension with isolated left ventricular diastolic dysfunction

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Background: Heart failure (HF) with preserved ejection fraction (HFpEF) is associated with LV structural and molecular abnormalities. These include LV hypertrophy and interstitial fibrosis (IF) that impair passive LV filling, and abnormal sarcoplasmic reticulum (SR) calcium cycling due to diminished calcium-ATPase (SERCA-2a) activity and phospholamban phosphorylation (p-PLB), which impair active LV relaxation. Bendavia, a novel mitochondria (MITO)-targeting peptide, was shown to improve LV systolic and diastolic function in dogs with HF. We hypothesized that the mechanisms underlying its effects on HF include improvement of key mediators of diastolic dysfunction.
Methods: 21 pigs were randomized to renovascular hypertension (RVH, n=14) or sham (normal controls, n=7). After 12 weeks, RVH pigs were again randomized to a 4-week therapy with Bendavia (0.1mg/kg SC, 5d/week, n=7) or saline (n=7). LV EF and the ratio of early (E) to late (A) relaxation (E/A), an index of diastolic function, were assessed by CT. LV muscle mass (LVMM), IF, SERCA-2a activity and p-PLB normalized to total PLB were quantified ex-vivo.
Results: RVH increased mean arterial pressure (MAP), LVMM, and IF, and decreased in E/A, SERCA-2a activity and p-PLB/PLB, without changing EF, suggesting isolated diastolic dysfunction (Table). In Bendavia-treated RVH pigs, LVMM, IF, E/A, SERCA-2a and p-PLB were all normalized, without changes in MAP or EF (Table).

Parameter (mean ± STD)	Normal-Control	RVH+Saline	RVH+Bendavia
MAP (mmHg)	79±4	123±4*	122±2*
EF (%)	59±10	60±7	61±6
E/A ratio	1.2±0.03	0.7±0.3*	1.0±0.2†
LVMM (g/kg)	1.7±0.3	2.5±0.4*	1.8±0.1†
IF (%)	0.9±0.7	2.2±2.1*	1.2±0.8†
SERCA-2a activity (nmol Pi released/min/mg)	854±126	392±39*	606±79†
p-PLB/PLB	1.02±0.20	0.32±0.09*	0.69±0.14†

*$p<0.05$ vs. Normal-Control; †$p<0.05$ vs. RVH+Saline.

Conclusions: In RVH pigs with LV diastolic dysfunction and preserved EF, therapy with Bendavia blunted myocardial hypertrophy and fibrosis and normalized SR calcium cycling. The results implicate MITO dysfunction in HFpEF etiology, and suggest Bendavia as a potential therapy in HFpEF.

P6563 | BEDSIDE
Association of circulating galectin-3 with exercise intolerance and left ventricular diastolic abnormalities in heart failure with preserved ejection fraction

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Galectin-3 (Gal-3) is a relevant mediator of myocardial fibrosis with a putative role in heart failure with preserved ejection fraction (HFpEF) as a causal factor contributing to a decrease in left ventricular (LV) compliance and elevation of filling pressure with resultant dyspnea. We sought to investigate the relationship of Gal-3 with reduced exercise capacity and abnormal LV filling pressure response to exercise in pts with HFpEF.
Methods: We enrolled 157 pts (age 65±9 yrs) with HFpEF (NYHA II–III,exercise capacity <80% of normal ranges, LVEF>50%, evidence of diastolic dysfunc-

tion) and 41 age-matched healthy controls. Cardiopulmonary exercise testing with echocardiographic assessment of myocardial function, including measurement of E/e' ratio approximating LV filling pressure, at rest and post-exercise were undertaken. Blood sampling included Gal-3 and BNP. According to the response of LV filling pressure to exercise, pts with HFpEF were stratified into 2 groups: with and without exertional increase in E/e'>13.
Results: Higher Gal-3 and lower exercise capacity were found in both subgroups with HFpEF, whereas higher BNP and resting E/e' and ΔE/e' (change from to rest to peak exercise) only in pts with post-exercise E/e'>13.HFpEF pts with post-exercise E/e'>13 had higher Gal-3 and lower exercise capacity than their peers with E/e'<13. In multivariable analysis,apart from patient age, BMI, LV mass, and presence of hypertension and diabetes, Gal-3 was an independent correlate of peak VO2 (β= -0.17,p<0.01), MET (β= -0.15, p<0.02), E/e' at rest (β=0.19, p<0.01) and post exercise (β=0.15, p<0.03) as well as ΔE/e'(β=0.15, p<0.04).

Results

	Post exercise E/e'>13 n=99 (1)	Post exercise E/e'<13 n=58 (2)	Controls n=41 (3)
Gal-3, ng/ml	1.30 (0.86–2.24)*&	0.81 (0.73–1.05)$	0.65 (0.59–0.98)
BNP, pg/m l	49.2 (25.5–118.3)*	30.5 (12.5–78.5)	32.5 (15.5–35.9)
Peak VO2, ml/min/kg	13.4±4.7*&	17.7±4.7&	25.4±3.6
ΔE/e'	4.8±4.4*&	0.3±3.3&	−1.0±2.2

$p<0.003 vs. (3); &p<0.001 vs. (3); #p<0.01 vs. (2); *p<0.001 vs. (2).

Conclusions: Increased Gal-3 is associated with reduced exercise capacity and increased LV filling pressure response to exercise in HFpEF, which underpins the contribution of myocardial fibrosis to the pathophysiology of this disease state. The detrimental clinical effect of fibrotic activation is particularly evident in pts with post-exercise E/e'>13,which may represent a suitable population for antifibrotic treatments.

P6564 | BEDSIDE
The pulmonary capillary wedge pressure accurately reflects both normal and elevated left atrial pressure

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Background: Pulmonary capillary wedge pressure (PCWP) is routinely used as an indirect measure of the left atrial pressure (LAP), although the accuracy of this estimate, especially under pathological haemodynamic conditions, remains controversial.
Objectives: The aim of this prospective study was to investigate the reliability of PCWP for the evaluation of LAP under different haemodynamic conditions.
Methods: Simultaneous left and right heart catheterization data of 117 patients with pure mitral stenosis, obtained before and immediately after percutaneous mitral comissurotomy, were analyzed.
Results: A strong correlation and agreement between PCWP and LAP measurements was demonstrated (correlation coefficient: 0.97, mean bias ± confidence interval (CI): 0.3 ± -3.7 to 4.2 mm Hg). Comparison of measurements performed within a 5 minutes interval and those performed simultaneously revealed that simultaneous pressure acquisition yielded better agreement between the two methods (bias ± CI: 1.82±1.98 mm Hg). In contrast to previous observations, the discrepancy between the two measures did not increase with elevated PCWP. Multiple regression analysis failed to identify haemodynamic confounders of the discrepancy between the two pressures. The ability of PCWP to distinguish between normal and elevated LAP (cutoff set at 12 and 15 Hg mm, respectively), as tested by receiver operating characteristics analysis, demonstrated a remarkably high diagnostic accuracy (area under curve: 0.989 and 0.996, respectively).
Conclusions: Although the described limits of agreement may not allow the interchangeability of PCWP and LAP, especially at lower pressure ranges, our data support the clinical utility PCWP as a robust and accurate estimate of LAP.

P6565 | BEDSIDE
Plasma leptin levels are associated with diastolic dysfunction in patients with coronary artery disease

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Purpose: Leptin is a peptide hormone derived mainly from adipose tissue. Obese subjects have elevated leptin levels, which have been associated with an increased risk of cardiovascular events. Because leptin has direct cellular effects on various tissues, we tested the hypothesis that leptin levels are associated with cardiac structure or function in patients with coronary artery disease (CAD).
Methods: The study population consisted of 1726 coronary artery disease patients of whom 43% had type 2 diabetes mellitus. Plasma leptin was measured in fasted state and an extensive cardiovascular examination was performed. Cardiac size and systolic function were measured from M-mode and 2-dimensional echocardiograms and diastolic function by the ratios of peak early diastolic mitral velocity to tissue Doppler-derived peak early diastolic mitral annular velocity (E/E'), peak early mitral velocity to peak atrial velocity (E/A) and integrated peak early mitral velocity to integrated peak atrial velocity (Ei/Ai).
Results: Plasma leptin levels were not related to left ventricular dimensions or left ventricular ejection fraction (NS for all), but higher leptin concentrations were associated with elevated E/E' (9.57 vs. 12.08 in the lowest and the highest leptin quartile, respectively; p<0.05 for trend). Correspondingly, a decreasing trend was observed in E/A (1.15 vs. 1.05 in the lowest and the highest leptin quartile, respectively; p<0.05 for trend) and Ei/Ai (1.65 vs. 1.42 in the lowest and the highest leptin quartile, respectively; p<0.05 for trend). All analyses were adjusted for age, sex, body mass index, waist-hip ratio, systolic blood pressure, heart rate during echocardiography, high-sensitivity C-reactive protein, stage of glucose metabolism disorder and history of myocardial infarction.
Conclusions: We conclude that elevated plasma leptin levels are associated with impaired left ventricular diastolic filling in patients with CAD independent of obesity and other confounding variables. Leptin may be one of the mechanistic links explaining the development of congestive heart failure of obese subjects.

P6566 | BENCH
The cardiac protease-activated receptor 2 expression is essential for the maintenance of the cardiac function in the aged heart

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Introduction: Elderly patients often suffer from left ventricular hypertrophy and diastolic dysfunction with preserved systolic function resulting from ongoing cardiomyocyte loss and cardiac fibrosis. The protease activated receptor (PAR) 2 is known to be a pro-fibrotic mediator. In a mouse model of myocardial infarction PAR2 overexpression in cardiomyocytes led to the development of fibrosis. In this study we examine the role of PAR2 in the aged heart regarding fibrosis and hemodynamic function.
Methods: 8 weeks (wks) and 1 year (yr) old wild-type (wt) and PAR2 knockout (ko) mice underwent hemodynamic measurements with a 1.2F microconductance catheter and hearts were collected for histological and biochemical analysis. Collagen release and Smad2 phosphorylation were determined with western blots and the ROS activity was analysed with a DCF dependent immunfluorescence assay on adult cardiac fibroblasts. The PAR2 gene expression was determined in myocardial biopsies from HFPEF patients.
Results: 1 year old PAR2ko mice suffered from a left ventricular dysfunction with preserved systolic function, which was accompanied by an age dependent fibrosis. In hearts of 8 wks old wt and PAR2ko mice no differences in collagen expression were present. In contrast, 1 yr old PAR2ko mice showed collagen depositions in the heart and the collagen I / collagen III ratio revealed a fibrosis in PAR2ko mice but not in wt mice (p<0.05). Moreover, adult cardiac PAR2ko fibroblasts also showed an increased collagen I release into the supernatant compared to wt fibroblasts. Furthermore, the TGFβ-dependent Smad2 phosphorylation was stronger in PAR2ko fibroblasts compared to wt fibroblasts. Oxidative stress in the heart often triggers cardiac dysfunction. After treatment with H2O2, PAR2ko fibroblasts exhibited higher ROS levels than wt fibroblasts (wt vs PAR2ko: 4.26±1.78 vs. 6.42±5.35, p<0.05). The GSH / GSSG ratio in hearts of 1yr hearts pointed also to an increased oxidative stress in PAR2ko mice compared to wt mice (wt vs PAR2ko: 8.31±2.59 vs. 4.80±1.53, p<0.05). These results indicate that the loss of PAR2 is associated with elevated oxidative stress, which leads to fibrosis and an impaired heart function. In HFPEF patients a decreased PAR2 expression was associated with severe diastolic dysfunction and vice versa.
Conclusion: The cardiac PAR2 expression is essential for the maintenance of the heart function in the aged heart. The loss of PAR2 results in increased oxidative stress, an age-dependent cardiac fibrosis and a left ventricular diastolic dysfunction.

P6567 | BENCH
Long-term therapy with Bendavia (MTP-131) reverses structural, cellular and molecular maladaptations responsible, in part, for left ventricular diastolic dysfunction in dogs with chronic heart failure

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Background: Several structural, cellular and molecular maladaptations that develop during the course of evolving heart failure (HF), act in concert to adversely impact left ventricular (LV) diastolic function. These key abnormalities include cardiomyocyte hypertrophy and reactive interstitial fibrosis both of which lead to increased LV stiffness and abnormal sarcoplasmic reticulum (SR) calcium cycling caused by diminished calcium-ATPase (SERCA-2a) expression and activity which directly leads to poor LV active relaxation. We previously showed that Bendavia (MTP-131), a novel mitochondria-targeting peptide, improves LV systolic and diastolic function in dogs with chronic HF by improving the rate of ATP synthesis by mitochondria. In the present study, we examined the long-term effects of Bendavia on these maladaptive factors considered responsible, albeit in part, for abnormalities of diastolic dysfunction in HF.
Methods: 14 dogs with coronary microembolization-induced HF were randomized to 3 months therapy with subcutaneous injections of Bendavia (0.5 mg/kg once daily, n=7) or saline (HF-Control, n=7). At end of the study, LV tissue was obtained from all study dogs and from 6 normal (NL) dogs. Cardiomyocyte cross-

sectional area (MCSA), a measure of cardiomyocyte hypertrophy, and volume fraction of interstitial fibrosis (VFIF) were assessed in LV free wall by histomorphometry. Protein levels of SERCA-2a were measured in LV homogenate using Western blotting and quantified in densitometric units (du).
Results: Compared to NL, HF-Controls showed significantly larger MCSA (410±10 vs. 678±5.4 μm^2), $p<0.05$), significantly greater VFIF (3.7±0.1 vs. 11.8±0.5%, $p<0.05$) and significantly lower protein levels of SERCA-2a (0.57±0.06 vs. 0.22±0.02 du, $p<0.05$). These abnormalities were associated with reduced indexes of LV diastolic function in HF-Controls compared to NL. Treatment with Bendavia ameliorated the increase in MCSA (600±4 μm^2, $p<0.05$), reduced VFIF (9.7±1.4%, $p<0.05$) and significantly increased protein levels of SERCA-2a (0.42±0.05 du, $p<0.05$) compared to HF-Controls. The benefits were associated with improved LV global indexes of diastolic function.
Conclusions: Long-term therapy with Bendavia ameliorates several key maladaptations implicated in diastolic dysfunction of the failing LV. These findings support the continued development of Bendavia as a potential therapy for patients with HF and LV diastolic dysfunction.

P6568 | BEDSIDE
Left atrial strain rate during isovolumic contraction predicts pulmonary capillary wedge pressure in patients with left ventricular systolic dysfunction

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Aim: The purpose of this study was to test the hypothesis that tissue Doppler (TD) derived left atrial strain rate (SR) during left ventricular (LV) isovolumic contraction predict pulmonary capillary wedge pressure (PCWP) in LV systolic dysfunction, and to compare left atrial SR between patients with heart failure and normal subjects.
Methods: Forty consecutive heart failure patients (56±8 years, 10 females (25%), all sinus), and 10 healthy controls were studied. Patients had echocardiography immediately before invasive catheter measurement of PCWP. TD derived left atrial SR during LV isovolumic contraction (SR-IC), LV ejection (SR-EJ), LV early diastole (SR-ED), and LV late diastole (SR-LD), were measured. Patients were classified according to their LV ejection fraction (EF) into 21 with EF<55%, and 19 with EF≥55%.
Results: All SR values were lower in the patient groups compared to controls (SR-IC: 1.46±0.62 vs. 2.42±0.37 1/s, $p<0.001$, SR-EJ: 1.91±0.77 vs. 3.75±0.65 1/s, $p<0.001$, SR-ED: 1.9±0.92vs. 5.1±0.73 1/s, $p<0.001$, SR-LD: 2.54±1.02 vs. 3.7±0.8 1/s, p=0.009). Moreover, patients with EF<55% had the lowest SR-IC and SR-EJ compared to patients with EF≥55% (1.25±0.6 vs. 1.72±0.57 and 1.5±0.5 vs. 2.4±0.8 1/s, p=0.04, 0.001) and controls ($p<0.001$), while SR-ED was not different between patients with EF<55% vs. EF≥55%, despite both being lower than that in the controls, and SR-LD was lower in EF<55% vs. controls, while was similar between EF≥55% and controls. Interestingly, the only variable that could overall significantly correlate with PCWP was SR-IC (r=0.567, $p<0.001$), while SR-EJ showed a weaker correlation (r=0.329, p=0.053), and SR-ED and SR-LD did not correlate with PCWP. SR-IC correlation with PCWP became excellent in EF<55% (r=0.715, p=0.001), while it was lost in EF≥55% (r=0.161, p=0.553). Other echocardiographic correlates with PCWP in EF<55% were: E/e' (r=0.523, p=0.013), left atrial volume (r=0.687, p=0.001), and mitral flow propagation velocity (r=0.585, p=0.008). Multivariate regression analysis revealed that SR-IC was the only variable that could independently predict PCWP in EF<55% (adjusted r2=0.552, beta= –0.469, p=0.04). ROC-curve suggested that SR-IC effectively predicts PCWP in EF<55% (AUC=0.9).
Conclusion: Left atrial SR values are impaired in all patients with heart failure symptoms, irrespective of the systolic function. SR-IC and SR-EJ are especially further impaired in patients with LV systolic dysfunction compared to those without, however, only SR-IC seems to effectively predict PCWP in patients with systolic dysfunction better than other echocardiographic variables

P6569 | BEDSIDE
Association between hs-cTnT and left ventricular diastolic dysfunction in a community-based elderly population of our country

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Purpose: Left ventricular diastolic dysfunction (LVDD) is characterized by impaired LV relaxation and increased diastolic LV stiffness. High-sensitivity cardiac troponin T (hs-cTnT) indicates the injury of cardiomyocytes, and could be a reliable indicator of myocardial remodeling. But whether hs-cTnT is related to LVDD is still unknown. We aimed to explore the association between hs-cTnT and LVDD in a community-based elderly population.
Methods: 1274 community residents (aged ≥65 years, 769 females) participating in a heart health study since 2007 were investigated. Echocardiography was used to evaluate diastolic function with conventional and tissue Doppler imaging techniques. The distribution of echocardiographic parameters and LVDD prevalence were analyzed according to tertiles of hs-cTnT levels. Multivariate logistic analysis was employed to investigate the relationship between hs-cTnT and LVDD.
Results: Hs-cTnT was higher in subjects with LVDD than those without [0.008 (0.005-0.012) vs. 0.007 (0.004-0.010) ng/mL, $P<0.001$]. Echocardiographic parameters incuding left atrial volume (LAV), LAV index, left ventricular end-diastolic diameter, interventricular septal thickness, posterior wall thickness and left ventricular mass index increased, while E/A ratio decreased, with the elevation of hs-cTnT (All $P<0.01$). The prevalence of LVDD also progressively increased with the elevation of hs-cTnT (33.6% when hs-cTnT <0.005 ng/mL, 39.1% when hs-cTnT between 0.005 and 0.01 ng/mL, 48.3% when hs-cTnT ≥0.01 ng/mL, $P<0.001$). Compared to hs-cTnT <0.005 ng/mL, the risk to present LVDD for subjects with hs-cTnT ≥0.01 ng/mL was obviously higher [Odds ratio (OR) 1.42, 95% confidence interval (CI) 1.03-1.95] after adjustment. Multivaraite logistic analysis revealed that hs-cTnT independently correlated with LVDD (OR 1.24, 95% CI 1.01-1.54).
Conclusions: Hs-cTnT was closely linked with LVDD in the community elderly population even at a very low level. This finding indicated a new marker and new mechanism of LVDD.

DIASTOLIC DYSFUNCTION II

P6571 | BEDSIDE
Lysyl oxidase-like-2 is expressed in patients with heart failure and preserved ejection fraction and correlated with the degree of fibrosis and inflammation in the heart

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Purpose: Lysyl oxidase-like-2 (LOXL2) belongs to the family of lysyl oxidase (LOX) and LOX-like proteins and promote cross-linking of fibrillar collagen I and fibrosis. Heart failure with preserved ejection fraction (HFPEF) is characterised by increased myocardial stiffness due to several mechanisms, among others due to increased collagen deposition and cross-linking of collagen fibers in the myocardium. We sought to examine the role of LOXL2 in HFPEF.
Methods: We investigated 41 patients (mean age 49±11.5) with normal ejection fraction (mean EF 59±9.5) whose endomyocardial biopsies were taken previously. Assessment of diastolic function was performed by mitral-flow and tissue Doppler measurements. Immunohistologic staining was performed to determine collagen I, cross-linking, LOXL2, LFA-1, ICAM-1 and VCAM-1 expression and CD3+ and MAC-1+ cells number.
Results: Twenty-six patients with HFPEF and diastolic dysfunction showed a significant increase in collagen I expression (30% higher, p=0.009) compared with that of 15 controls. LOXL2-expression was 2.5times higher in HFPEF patients compared to controls (p=0.023). This was associated with significantly higher cross-linking of collagen fibers in HFPEF patients by 1.8times (p=0.03) compared to controls. Furthermore, HFPEF patients showed increased inflammation as measured by 2times higher CD3+ cells (p=0.04), 1.7times higher ICAM-1 expression (p=0.03), 3times higher VCAM-1 expression (p=0.015) and 2times higher LFA-1 expression (p=0-0135). There was no significant difference in the amount of MAC-1+ cells between the 2 groups.
The expression of LOXL2 correlated significantly with the protein expression of collagen I (r=0.49, p=0.033), the amount of cross-linking (r=0.67, p=0.0087), the amount of CD3+ cells (r=0.47, p=0.04) and LFA-1 (r=0.5, p=0.017) but not with MAC-1+ cells, ICAM-1 or VCAM-1 expression.
Conclusions: LOXL2 shows a significantly higher expression in the myocardium of patients with HFPEF compared with patients without HFPEF and correlated with the amount of myocardial fibrosis and inflammation. LOXL2 might be a new target for reduction of fibrosis and inflammation in HFPEF patients.
Conclusions: LOXL2 shows a significantly higher expression in the myocardium of patients with HFPEF compared with patients without HFPEF and correlated with the amount of myocardial fibrosis and inflammation. LOXL2 might be a new target for reduction of fibrosis and inflammation in HFPEF patients.

P6572 | BENCH
NOS/redox-independent protective effects of GTP cyclohydrolase 1 (GCH1) overexpression and tetrahydrobiopterin (BH4) in diabetic cardiomyopathy

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Purpose: Diabetic cardiomyopathy is characterised by the early onset of significant left ventricular (LV) diastolic dysfunction, the origin of which remains poorly understood. Oxidative stress and reduced nitric oxide (NO) bioavailability secondary to BH4 oxidation underlie the endothelial dysfunction observed in all types of diabetes; however, whether an altered myocardial NO-redox balance accounts for the diabetic cardiomyopathy phenotype remains to be established. We addressed these issues in a murine model of type 1 diabetes and evaluated the effect of inducing a myocardial-specific increase in BH4 in the development of LV dysfunction
Methods: Diabetes was induced by streptozotocin injection (43mg/kg; for 5 days). After 12 weeks we evaluated vasomotor function in aortic rings by wire myo-

graphy, nitric oxide synthase (NOS) activity and biopterins by HPLC, superoxide production by lucigenin-enhanced chemiluminescence, myocardial collagen content by colorimetry, and LV performance by echocardiography. A myocardial-specific increase in BH4 was obtained by transgenic overexpression of human GTP-cyclohydrolase 1 under the αMHC promoter (mGCH1Tg)
Results: Vasomotor studies in both WT and mGCH1Tg showed impaired aortic endothelium-dependent vasodilatation, in association with increased superoxide production and reduced BH4 (n=6-10). By contrast, LV homogenates from diabetic WT and mGCH1Tg mice showed no evidence of an increase in superoxide generation or of a reduction in BH4 and total NOS activity. Nevertheless, in vivo echocardiography showed that the significant LV diastolic dysfunction observed in WT diabetic mice was prevented in mGCH1Tg mice (E'/A' diabetic vs control: 1.52±0.08 vs. 1.53±0.08 in mGCH1Tg and 0.89±0.07 vs. 1.35±0.06 in WT, n=9, $P<0.01$ for the interaction between genotype and diabetes). In line with these results, isolated LV myocytes from WT diabetic mice displayed prolonged relaxation which was prevented in diabetic mGCH1Tg (t50 in ms, diabetic vs control: 105.3±2.8 vs. 95.6±2.4 in WT and 77.3±3 vs. 73.3±2 in mGCH1Tg, n=25-46, $P<0.05$ for the interaction between genotype and diabetes). LV collagen content was significantly increased in both WT and mGCH1Tg diabetic mice, indicating that increasing myocardial BH4 preserved LV diastolic function without preventing the development of fibrosis
Conclusions: Impaired LV diastolic function in diabetic mice can be prevented by myocardial GCH1 overexpression in the absence of NOS dysfunction or increased oxidative stress, suggesting that GCH1/BH4 protect the diabetic myocardium by mechanisms other than redressing the local nitroso-redox balance

P6573 | BEDSIDE
Elevation of circulating fatty acid-binding protein 4 is associated with left ventricular diastolic dysfunction in a general population

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Purpose: Fatty acid-binding protein 4 (FABP4) is expressed in both adipocytes and macrophages. Recent studies have shown secretion of FABP4 from adipocytes and association of elevated serum FABP4 level with obesity, insulin resistance, and atherosclerosis. However, little is known about role of FABP4 in cardiac function.
Methods: From database of the Tanno-Sobetsu Study, data for 190 subjects (male/female: 82/108) who were treated with no medication and underwent echocardiography in 2011 or 2012 were retrieved for analyses of relationships between serum FABP4 concentration, metabolic markers and parameters of echocardiography.
Results: Serum FABP4 level was positively correlated with age, body mass index (BMI), blood pressure (BP), LDL cholesterol and HOMA-R and was negatively correlated with HDL cholesterol, estimated glomerular filtration rate (eGFR) and peak myocardial velocity during early diastole (e'; male: r = -0.434, female: r = -0.353, $p<0.01$), an index of LV diastolic function. However, no significant correlation was observed between FABP4 level and LV end-diastolic dimension, LV ejection fraction or LV mass index. There were significant correlations of e' with age, BMI, BP, eGFR, brain natriuretic peptide (BNP), FABP4, and metabolic markers. Multivariate regression analysis adjusted by HOMA-R, BMI, eGFR, BNP or left ventricular wall thickness in addition to age, gender and BP revealed that serum FABP4 concentration was independently correlated with e'.
Conclusions: Elevation of circulating FABP4 may contribute to LV diastolic dysfunction via a hypertrophy-independent mechanism in a general population.

P6574 | BEDSIDE
Association of obstructive sleep apnea with diastolic dysfunction with elevated left ventricular filling pressure in coronary artery disease patients with preserved ejection fraction

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Purpose: We addressed if diastolic dysfunction with elevated left ventricular (LV) filling pressure was associated with obstructive sleep apnoea (OSA) in a cohort of patients with coronary artery disease (CAD) and preserved LV ejection fraction. The study was carried out within the framework of a randomized controlled trial (RICCADSA), which evaluates the impact of continuous positive airway pressure on cardiovascular outcomes in CAD patients with concomitant OSA,
Methods: Baseline sleep study recordings and echocardiographic measurements of 431 revascularized patients with CAD (age 63.7±8.8 yrs; 82.5% men) with LV ejection fraction ≥50% were evaluated. OSA patients (n=331) had Apnea-Hypopnea-Index (AHI) ≥15 events/h, and non-OSA patients (n=100) had AHI<5 events/h. Diastolic dysfunction with elevated LV filling pressure was defined as peak flow velocity in early diastole (E)/Tissue Doppler of early diastolic ventricular filling (é) >13 cm/s, or E/é<9 cm/s and a left atrium diameter of ≥39 mm for women, or E/é<9 and a left atrium diameter of ≥40 mm for men.
Results: Diastolic dysfunction with elevated LV filling pressure was more common among the OSA group (54.4% vs 41.0%, p=0.019). In a multivariate analysis, OSA was associated with diastolic dysfunction with elevated LV filling pressure (odds ratio [OR] 1.90, 95% confidence interval [CI] 1.13;3.18) adjusted for female gender (OR 2.28, 95% CI 1.28;4.07), hypertension (OR 1.84, 95% CI 1.20;2.82), diabetes mellitus (OR 2.45, 95% CI 1.42;4.23), age≥60 yrs (n.s), obesity (n.s.) and current smoking (n.s.).
Conclusions: In this CAD cohort with preserved LV ejection fraction, diastolic dysfunction with elevated LV filling pressure was associated with OSA independent of the traditionally recognized risk indicators.

P6575 | BEDSIDE
A good left ventricular diastolic performance is predictive of better outcome in young subjects in early phase of hypertension

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Objective: Echocardiographic data are important predictors of outcome in hypertension but it is not clear which echocardiographic parameters have better prognostic capacity in particular in young subjects in stage I hypertension. In the present study we assessed the predictive value of structural and functional echocardiographic parameters for the development of hypertension in a cohort of young-to-middle-age subjects from the HARVEST study.
Methods: 674 adults (501 men, age=33±8 years) screened for stage 1 hypertension were considered. Patients were seen every six months to determine which subjects developed hypertension needing therapy according to current guidelines (HT). Echocardiography and ambulatory blood pressure (BP) monitoring were performed at entry. Left ventricular (LV) mass index, relative wall thickness, LV stress, LV ejection fraction, and the E/A ratio as a measure of LV diastolic function were calculated. The predictive value of echocardiographic data was assessed in multivariable Cox analyses, adjusting for age, gender, body mass index, 24-hour systolic or diastolic BP, and lifestyle factors.
Results: During a median follow-up of 13.5 years 64.5% of the subjects developed HT. In a multivariable Cox analysis, 24-h systolic BP (p=0.0009), 24-h diastolic BP (p=0.0005), coffee consumption (p=0.008), and the E/A ratio (inverse association, p=0.004) were independent predictors of outcome. None of the other echocardiographic parameters were associated with the risk of HT. In the subjects divided into quintiles of E/A ratio, an increase in the rate of HT was observed on going from the top (52%) to the bottom (70%, p for trend=0.0006) E/A quintile with a tendency to an inverted L-shaped relationship. Having an E/A ratio ≥1.68 (lower limit of the top quintile) showed a protective effect on the risk of HT compared to the subjects of the bottom quintile (hazard ratio= 0.57, 95%CI = 0.41–0.80, p=0.001).
Conclusions: These data show that a good LV diastolic performance is a better predictor of outcome in young subjects screened for stage 1 hypertension on the other hand structural and functional echocardiographic parameters are not predictive of outcome in this setting.

P6576 | BEDSIDE
Relationship between left atrial volume and diastolic dysfunction in Nigerian hypertensives

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Purpose: This study was designed to determine the usefulness of left atrial volume index (LAVI) as a surrogate marker of left ventricular diastolic dysfunction in Nigerian hypertensives.
Methods: Hypertensive subjects attending a cardiology practice in South Western Nigeria who were in sinus rhythm without a history of atrial arrhythmia or valvular heart disease and age and sex matched normotensive controls were recruited for the study. Transthoracic echocardiography was conducted for all the participants. Doppler indices of diastolic function were assessed and left atrial volume was measured using the biplane area length method and further indexed to body surface area. Associations between LAVI and diastolic dysfunction were examined.
Results: There were 200 subjects and 100 controls (age 55.8±11.4 vs 55.7±11.0yrs, p=0.92). The subjects had higher systolic blood pressure (SBP) and diastolic blood pressure (DBP), 141.1±23.6 vs 112.6±6.6mmHg and 84.8±14.9 vs 71.4±6.7mmHg, $p<0.0001$ respectively. The subjects also had significantly higher BMI than the controls, 27.3±5.0 vs 25.7±5.1, p=0.004. Among the subjects, 70% had left atrial enlargement (LAE) and 80% had diastolic dysfunction (DD). Mean LAVI was significantly higher in the hypertensives with DD than in the hypertensives with normal diastolic function, 38.5±10.4 mL/m^2 vs 30.6±9.2 mL/m^2, $p<0.0001$. The LAVI increased significantly with worsening diastolic dysfunction; 30.6±9.2 mL/m^2 (normal diastolic function), 37.9±10.5 mL/m^2 (grade I DD), 38.5±8.3 mL/m^2 (grade II DD), 49.4±15.5 mL/m^2 (grade III-IV DD) (p=0.0001). Left atrial volume index was found to correlate positively with age, duration of hypertension, SBP, DBP, LV mass, and diastolic function grade. In a multivariate model, LAVI was independently associated with age, LV mass, female gender, DD and abdominal obesity. An LAVI of >31.2 mL/m^2 was found to predict the presence of left ventricular diastolic dysfunction with 76.3% sensitivity and 55% specificity. The area under the receiver operator characteristic curve for

LAVI to detect grade I, grade II, and grade III to IV DD was 0.70, 0.75 and 0.87 respectively, showing a progressive increase with worsening DD. Left atrial volume index performed better than LA linear M-mode dimensions in the detection of diastolic dysfunction.
Conclusions: Diastolic dysfunction is common in Nigerian hypertensives and LAE is highly prevalent in hypertensives with diastolic dysfunction. Left atrial volume index predicts the presence of diastolic dysfunction and has a graded increase with worsening diastolic dysfunction in Nigerian hypertensives.

P6577 | BEDSIDE
High resting heart rate as a risk factor of recurrent hospitalisations in heart failure with preserved ejection fraction: results of the Preserved-DATA-HELP registry

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Background: High resting heart rate (HR) is common in patients with systolic heart failure (HF) and associated with poor outcome. Its reduction due to both β-adrenergic and I(f) current blockade has provided survival benefits in these patients. We investigated the prevalence of high resting HR in patients with HF with preserved ejection fraction (HFPEF), as well as links with clinical profile, applied treatment and hospitalisation rates.
Methods: During the DATA-HELP registry performed in 2009 in Poland among cardiologist and general practitioners outpatient clinics, we collected the data on 488 patients with HFPEF in a sinus rhythm with available resting HR (age: 67±11 y, men: 52%, BMI: 28.5±4.0 kg/m^2, LVEF: 52±5%, NYHA class III-IV: 17%, CCS class III-IV: 15%, previous MI: 45%, hypertension: 75%, diabetes: 32%).
Results: Among patients with HFPEF, a mean resting HR was 75±12 bpm with a median (lower and upper quartiles) of 75 (68-80) bpm. High resting HR ≥70 bpm and ≥75 bpm were found in 71% and 51% of patients, respectively, regardless on NYHA class ($p>0.2$) and although 96% of them received β-blockers. Treatment with either β-blockers or Ca2+ channel blockers did not differentiate resting HR (all $p>0.2$). Moreover, there were no associations between resting HR, and daily doses of particular β-blockers and Ca2+ channel blockers (all $p>0.2$). Lower CCS class, higher systolic blood pressure, jugular venous dilatation, female gender and the treatment by general practitioner were independent predictors of high resting HR (all $p<0.05$). The higher the number of urgent cardiovascular hospitalisations during recent 12 months, the higher resting HR (for 0, 1-3 and ≥4 hospitalisations - mean HR: 74±10, 75±12 and 87±17 bpm - $p<0.01$, HR ≥75 bpm: 45%, 54% and 88%, p=0.03). Also, the higher the number of other elective hospitalisations during recent 12 months, the higher resting HR (for 0, 1-3 and ≥4 hospitalisations: mean HR: 75±10, 76±14 and 91±9 bpm - $p<0.001$, HR ≥75 bpm 51%, 49% and 91%, p=0.03).
Conclusions: High resting HR is found in the majority of patients with HFPEF, regardless of NYHA class and therapies with β-blockers or/and Ca2+ channel blockers. High resting HR is associated with increased recent hospitalisation rates. Given these findings, HR reducing therapies and their effects on hospitalisation rates could be considered in patients with HFPEF.

P6578 | BEDSIDE
Left ventricular involvement in type I gaucher disease

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Purpose: Type I Gaucher Disease (GD) is an autosomal recessive lysosomal storage disease characterized by multi-organ involvement. Right ventricular overload due to pulmonary hypertension is the most frequent cardiac manifestation, whereas a clear-cut left ventricular (LV) involvement has been reported only in a few cases of advanced disease stages. Accordingly, aim of the study was to evaluate LV geometry and function in a series of patients with GD.
Methods: Seventeen patients with Type I Gaucher Disease (GD) (median age = 46 yrs, interquartile range = 39–50), 17 age and sex-matched normal controls (NC) and 17 age and sex matched hypertensive patients (HT) were compared by standard echo-Doppler examination. LV mass index (g/m$^{2.7}$), relative wall thickness and ejection fraction (%) were determined by 2D echo. Transmitral E/A ratio, deceleration time of E velocity (DT, ms), atrial filling fraction (AFF = velocity time integral of A velocity / velocity time integral of total diastole x 100, %), E/e' ratio and left atrial volume index (LAVi, ml/m^2) were measured as indicators of LV diastolic function. Between-group comparison was carried out using Kruskal-Wallis test and ANCOVA.
Results: The 3 groups were comparable for body mass index, whereas heart rate was higher in HT ($p<0.05$). Eight GD patients also exhibited arterial hypertension. The intergroup difference of LV mass index and relative wall thickness was not significant. Transmitral E/A ratio was lower in HT (1.1±0.3) than NC (1.4±0.3, p=0.04) whereas no difference was observed in GD (1.1±0.4). Differences in AFF, E/e' and LAVi did not achieve statistical significance. GD exhibited longer DT (219.5±43.5 ms) than NC (188.7±33.4 ms) and HT (188.9±30.7 ms, $p<0.04$). After adjusting for heart rate and systolic blood pressure (ANCOVA), DT was confirmed to be significantly prolonged in GD ($p<0.01$). Additional analyses did not reveal any significant difference of E/A, DT, AFF, E/e' and LAVi in subgroups of GD with or without arterial hypertension.
Conclusion: Type I Gaucher disease is associated with subclinical LV diastolic dysfunction which is independent on the possible coexistence of hypertension. Early LV impaired relaxation in the context of myocardial infiltrative damage could be the mechanism underlying these alterations.

P6579 | BEDSIDE
Value of diastolic function indexes during exercise echocardiography to predict outcome when mitral regurgitation information is available

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The ratio of left ventricular (LV) inflow early wave and tissue Doppler annulus early wave (E/e') is a subrogate of LV filling pressures that can be assessed during exercise (Ex). Previous work has demonstrated the value of the increase of this ratio with Ex to predict outcome. We sought to assess the relative value of E/e' during Ex-echocardiography (ExE) to predict outcome when information about mitral regurgitation (MR) at rest (R) and at Ex is available. Also we compared the value of the E/e'ratio to that of a change to a pseudonormalized (Ps) LV filling pattern during Ex.
Methods: ExE with assessment of MR, LV inflow patterns and E/e'at rest and at exercise were performed in 470 patients (298 men; age 62±12 years). An exercise Ps pattern was defined as the persistence of a resting Ps pattern, or a change from a normal/altered relaxation pattern to a Ps pattern. Considered hard events were non-fatal myocardial infarction (MI) and overall mortality, and considered combined events were a hard event, stroke or late revascularization [≥3 months after ExE]. Cox regression analysis was performed to assess predictors of the end-points by a time to first event basis.
Results: There were 63 hard events (34 non-fatal MI and 29 deaths) and 85 combined events during a mean follow-up of 1.8±2.2 years. Independent predictors of combined events were a history of coronary artery disease (hazard ratio [HR]=1.88, 95% confidence interval [CI]= CI=1.19-2.98, p=0.007), treatment with digoxin (HR=10.41, 95% CI=2.42-44.89, p=0.002), resting MR (HR=1.10, 95% CI=1.03-1.17, p=0.003), achieved workload in METs (HR=0.90, 95% CI=0.84-0.98, p=0.009), clinical symptoms during ExE (HR=1.94, 95% CI=1.19-3.14, p=0.007), positive ECG (HR=1.94, 95% CI=1.16-3.24, p=0.01) and increase in MR with Ex (HR= 1.11, 95% CI=1.02-1.21, p=0.02). E/e'ratios and Ps patterns at R and at Ex were associated to combined events by univariate analysis and exhibit a trend to be associated by multivariate analysis when MR information was not taken into account, but lost their values when this information was considered. By receiver operator (ROC) curves their values for predicting events were similar at rest (Ps pattern vs. E/e', 0.45 vs. 0.55) and at Ex (Ps pattern 0.57; E/e'0.61).
Conclusions: In conclusion, the prognostic value of LV diastolic indexes for predicting outcome seems limited when strong information based on MR is available during ExE.