Relation between blood pressure lowering therapy and cardio-vascular events and mortality in hypertensive patients with coronary artery disease and type 2 diabetes: the HIU-CREATE sub-study

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Purpose: To explore the optimal systolic blood pressure target in hypertensive patients with coronary artery disease (CAD) and type 2 diabetes in the subsity of the HIU-CREATE trial.

Methods: HIU-CREATE was a multicenter, prospective, randomized, controlled study that compared the effects of candesartan-based therapy with those of non-ARB-based standard therapy on MACE in 2,049 hypertensive patients with angiographically documented CAD. Of the 2,049 participants, 780 (38.1%) were complicated with type 2 diabetes. In both groups, titration of antihypertensive agents was performed to reach the target blood pressure (BP) of <130/85 mmHg. The primary endpoint was the time to first major adverse cardiac events (MACE). The incidence of endpoint events in addition to biochemistry tests and office BP was determined during the schedule of 6, 12, 24, 36, 48, and 60 month visits. Achieved BP were defined as the mean value of systolic BP in patients who did not meet with MACE and the mean value of systolic BP prior to MACE in those who met with MACE during follow-up.

Results: During a mean follow-up of 4.2 years (follow-up rate of 99.6%), the primary outcome occurred in 259 (33.2%) diabetic patients and in 293 (23.1%) non-diabetic patients (p < 0.0001). The participants were divided into equal quartiles based on the mean systolic BP during follow-up. The relationships between achieved systolic BP and the incidence of MACE did not follow J-shaped curves in both groups (Figure).

Conclusions: The present study suggests that the excessive BP lowering regimen of the contemporary era causes no harm even in high risk population. Nonetheless, along with BP lowering therapy, the establishment of an optimal management strategy for hypertensive CAD patients with diabetes is essential.

The effect of visit-to-visit variability in blood pressure on stroke and coronary events in the TNT, IDEAL and CARDS trials

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Purpose: It has been proposed that visit-to-visit variability in systolic blood pressure (SBP) predicts CV risk independently of mean SBP. This study assessed the association between visit-to-visit variability in BP and the risk of CV events (CVE) among high-risk patients in the TNT, IDEAL and CARDS trials, and investigated whether BP and variability contributed to differences in clinical benefits observed with different statin treatment regimens.

Methods: We followed up 1128 essential hypertensives (mean age 56.1 years, 61 years) in the TNT, 2029 in the IDEAL, and 2027 in the CARDS studies. Variability of SBP and DBP were assessed by calculating the standard deviation (SD) of each individual’s SBP or DBP at each visit (SDBP and SDDBP, respectively). The effect of variability on CVE was evaluated by Cox regression analysis.

Conclusions: The present study suggests that the excessive BP lowering regimen of the contemporary era causes no harm even in high risk population. Nonetheless, along with BP lowering therapy, the establishment of an optimal management strategy for hypertensive CAD patients with diabetes is essential.

Low attenuation coronary plaque on multidetector computed tomography predicts three-year acute coronary syndrome events in patients with hypertension

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Purpose: Arterial hypertension is an established risk factor for acute coronary syndrome (ACS). Multidetector computed tomography (MDCT) is an accurate and less invasive technique for assessment of the degree of coronary artery lumen narrowing and characterization of coronary atherosclerosis. We therefore aimed to investigate the predictive power of MDCT for ACS events and compared with traditional parameters in patients with hypertension.

Methods: One hundred and thirty-four patients (93 mm, mean age 70 ± 11 years) with hypertension underwent MDCT for evaluation of coronary artery disease. MDCT analysis focused on the presence of plaques, the degree of stenosis, and the plaque characteristics. Traditional parameters included Framingham risk score (FRS), carotid intima-media thickness (IMT), and left ventricular mass index (LVM).

Results: During a mean follow-up of 3.3 years, ACS events occurred in 10 patients. In the multivariate analysis, the number of low attenuation plaque (LAP) was identified as an independent predictor of ACS events (p < 0.001). Case examples are presented in Figure. Curved multiplanar reconstruction image of right coronary artery demonstrated the presence of LAP (arrows) (Figure A), which developed ACS event 3 years after MDCT examination (Figure B). Increased events rate was observed in patients with ≥2 LAP compared with those without LAP (p < 0.001) (Figure C). There were no significant differences between patients with and without ACS events in the FRS, carotid IMT, LVM, and any of the laboratory parameters.

Conclusions: We demonstrated that LAP on MDCT predicted more accurately future ACS events in patients with hypertension than traditional parameters.

Pulse wave velocity as independent predictor of stroke in patients with essential hypertension: data from a Greek 6-year-follow-up study

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Purpose: Although arterial stiffening is related to atherosclerosis progression, its prognostic role in cerebrovascular events in hypertension is not fully elucidated. The aim of the present study was to assess the prognostic role of arterial stiffness for the incidence of stroke in a cohort of essential hypertensive patients.

Methods: We followed up 1128 essential hypertensives (mean age 56.1 years, 587 males, office blood pressure (BP) ≥144/91 mmHg) free of cardiovascular disease for a mean period of 6 years. All subjects had at least one annual visit and at baseline undertaken blood sampling for assessment of metabolic profile and arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior SP). The distribution of
PWV was split by the median (8.1 m/sec) and accordingly subjects were classified into those with high (n=566) and low values (n=562). Stroke was defined as rapid onset of a new neurological deficit persisting at least 24 hours unless death supervened confirmed by computed tomography and magnetic resonance angiography and/or cerebrovascular angiography findings.

**Results:** The incidence of stroke over the follow-up period was 2.03%. Hypertensives who had stroke (n=23) compared to those without stroke at follow-up (n=1105) were older at baseline (63±8 vs 55±10 years, p=0.015), had higher office BP levels (155 vs 13 ± 143±17 mmHg, p=0.018) and prevalence of high PWV levels (67% vs 43%, p=0.021). No difference was observed between hypertensives with stroke and those without stroke with respect to baseline renal function and lipid levels (p=NS for all). By univariate Cox regression analysis it was revealed that high baseline PWV levels predicted stroke (hazard ratio=1.307, p=0.014). Moreover, in multivariate Cox regression model, baseline age (hazard ratio=1.098, p=0.03) and PWV (hazard ratio=1.125, p=0.017) but not baseline office BP levels turned out to be independent predictors of stroke.

**Conclusions:** In essential hypertensive patients, PWV predicts future development of stroke, independently of age and office BP. These findings support that PWV constitutes a potent prognosticator of cerebrovascular events and its estimation is essential in order to improve risk stratification in hypertension.

**3786 Prediction of cardiovascular events and all-cause mortality with brachial-ankle pulse wave velocity: a systematic review and meta-analysis of cohort studies**

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**Purpose:** Brachial-ankle pulse wave velocity (baPWV) is increasingly recognized as a surrogate end-point for cardiovascular (CV) disease. We performed a meta-analysis of all longitudinal cohort studies for determining the ability of baPWV to predict risk of CV events and all-cause mortality.

**Methods:** The MEDLINE, Cochrane and EMBASE databases, and reviewing reference lists from retrieved articles and abstracts from large international cardiovascular vascular conceptions were searched until January 2012. Longitudinal cohort studies that reported relative risk (RR) estimates with 95% confidence intervals were included. Reviewers extracted data independently and summary estimates of association were obtained using a fixed- or random-effects model. Risk estimates between subgroups were compared with an interaction test.

**Results:** Of the 17 studies included (8,217 participants, mean follow-up 3.37 years), 14 reported results on total CV events (5,406 individuals), 6 on CV mortality (2,139 individuals) and 9 on all-cause mortality (5,132 individuals). The pooled relative risks (RRs) for total CV events, CV mortality and all-cause mortality were 2.77 (95% confidence interval: 1.91 to 4.01) (Figure), 7.37 (95% CI: 3.67 to 14.79) and 2.62 (95% confidence interval: 1.87 to 3.66), respectively, for subjects with high baPWV versus subjects with low baPWV. For total CV events, the RR was significantly higher in high baseline risk groups (heart disease, renal disease, hypertension, diabetes) compared with low-risk subjects (general population). An increase in baPWV by 1 m/sec corresponded to an increase of 17% in total CV events.

**Conclusions:** baPWV is associated with increased risk of total CV events and all-cause mortality. Predictive value of baPWV for total CV events is increased in general population.

**3787 Influence of family history of hypertension and hypertension per se on overall and cardiovascular mortality in the Seven Countries Studies: the 40 years follow up results**

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**Purpose:** The Seven Countries Study is one of the landmark epidemiological studies that encompassed 12 cohorts in 7 countries with a total of over 10,000 men in a follow up going beyond 4 decades with a response rate nearing 95% worldwide. Its meticulously detailed design and systematic follow up, enables us to assess different aspects of the presence and impact of traditional risk factors on a myriad of outcomes. In this particular case, we sought to determine influence of family history of hypertension and hypertension per se on overall and coronary artery disease (CAD) mortality.

**Methods:** All subjects enrolled in the 3 Serbian cohorts of the Seven Countries' Study, were men aged 40-59 years at entry (1962-1964) who were subsequently followed every 5 years.

**Results:** Of 1565 men, aged 48.53 years, 1298 deaths of known cause (82.9%) were available for further analysis, while data on presence of hypertension and family history of hypertension was available for all. Looking at overall mortality, 992 participants were hypertension free at entry, out of which 82% were deceased at the closure of the 40 years follow up, with 27 years' survival; while of the 573 participants with hypertension at entry, 92.7% had a 23 years' survival (logrank=76.067, p<0.001). In those who had hypertension, but also carried a burden of family history of hypertension (118 participants), survival was 24 years for 93.2% of the deceased, while for those who were free of parental hypertension (124 participants), survival was 30 years for 74.2% of the deceased. When CAD mortality has been additionally looked into, 24.1% of the hypertension-free participants (992) had a 35 years survival, while for those with hypertension, 26.5% of the 573 participants had a 33 years survival.

**Conclusion:** In the Serbian cohorts of the Seven Countries Study, as a result of the 40 years follow up, we have shown that participants who were hypertension-free at entry, had a longer life expectancy, both for overall and CAD mortality – 4 years and 2 years, respectively, while for those who had hypertension and whose family history was also remarkable for hypertension, survival was shorter for 6 years.

**3792 Validation and clinical application of systolic and diastolic central pressures derived from pulse wave analysis**

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**Purpose:** The use of surrogate measures for central artery blood pressure (BP) is now commonplace, including radial artery pulse wave analysis (PWA). Prior studies have examined central augmentation index (cAI), defined as the systolic augmentation pressure (cAP)/pulse pressure. We sought to assess the validity, reproducibility and clinical utility of systolic and diastolic parameters.

**Methods:** Patients attending elective coronary angiography were pre-assessed with conventional sphygmonanometry and radial PWA. Direct aortic BP was taken during catheterisation in 346 participants of the ARM-CAD study.

**Results:** PWA-derived central systolic BP was closer to measured pressure (2.70mmHg lower; SE=1.18) compared to conventional BP (8.03mmHg higher; SE=1.22). However for diastolic BP, conventional and PWA measurement were similar and higher than aortic (9.93; SE=0.83 and 10.99; SE=0.83mmHg) resulting in significant differences in pulse pressure (see figure). cAP was linearly related to central systolic pressure with a standard error of 0.8% (p=0.001). The AUC for cAP was 0.92 (95% CI: 0.89 to 0.95) with a cut-off of 2.75 mmHg lower than aortic pressure.

**Conclusions:** The use of central BP measures is feasible and accurate compared to conventional sphygmomanometry. cAP was a useful parameter in the validation and clinical application of pulse wave analysis.
associated with age (r=0.40, p<0.001), whereas pulse pressure and cAI had a curvilinear relationship. All three PWA variables were reproducible in repeated measurements (correlation coefficients >0.9, coefficients of variation 9-11%). CAP derived solely from systole, was significantly decreased by angiographic coronary disease after adjusting for risk factors (odds ratio 95% CI 1.15-6.12; p<0.02), unlike cAI (0.90-2.24; p=0.13).

**Conclusion:** Variation in diastolic parameters limits the use of pulse pressure and augmentation index for risk stratification. However, radial artery PWA is a valid and reproducible method of estimating central systolic BP and associated variables such as augmentation pressure, which is independently associated with coronary atherosclerosis.

**Methods:** In 1266 Japanese men without hypertension (43.6±8 years old), the relationships of the baPWV and second peak of the radial pressure waveform (SP2) measured at the first examination with the presence of hypertension at the second examination (after 3 years’ follow-up) were examined. Hypertension was detected at the second examination in 154 men. Estimated areas under the curve to predict the presence of hypertension at the second examination were as follows: brachial-ankle PWV at the first examination = 0.716 and SP2 at the first examination = 0.843. The best cutoff point of the baPWV and SP2 for predicting the development of hypertension than a baPWV of >12.7 m/sec, independent of other covariates including the first peak of the radial pressure waveform. The net reclassification index of this cutoff point of SP2 for predicting the development of hypertension that of the baPWV was 0.211 (p<0.001).

**Conclusion:** In middle-aged Japanese men without hypertension, SP2 may be a more powerful predictor of the development of hypertension than the baPWV, independent of the conventionally known risk factors for the development of hypertension.

**Central blood pressure: a possible powerful predictor of the development of hypertension**

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**Aims:** Vascular mechanisms are known to have vital roles in the development of hypertension. We examined whether the central aortic systolic blood pressure, a marker of function in systemic arterial tree, might be a more powerful predictor of the development of hypertension as compared with the brachial-ankle pulse wave velocity (baPWV), a marker of stiffness in large to middle-sized arteries.

**Methods and Results:** In 1266 Japanese men without hypertension (43.6±8 years old), the relationships of the baPWV and second peak of the radial pressure waveform (SP2) measured at the first examination with the presence of hypertension at the second examination (after 3 years’ follow-up) were examined. Hypertension was detected at the second examination in 154 men. Estimated areas under the curve to predict the presence of hypertension at the second examination were as follows: brachial-ankle PWV at the first examination = 0.716 and SP2 at the first examination = 0.843. The best cutoff point of the baPWV and SP2 for predicting the development of hypertension than a baPWV of >12.7 m/sec, independent of other covariates including the first peak of the radial pressure waveform. The net reclassification index of this cutoff point of SP2 for predicting the development of hypertension that of the baPWV was 0.211 (p<0.001).

**Conclusion:** In middle-aged Japanese men without hypertension, SP2 may be a more powerful predictor of the development of hypertension than the baPWV, independent of the conventionally known risk factors for the development of hypertension.

**N- terminal fragment of brain natriuretic peptide predicts vascular health and subclinical atherosclerosis: results from MEHLP study**

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**Background:** Evaluation of subclinical atherosclerosis and vascular health have been used to predict cardiovascular events. Several indexes have been evaluated, i.e. coronary artery calcium score (CCS) by computed tomography scan (CT), intima-media thickness (IMT) of common carotid artery and ascending aorta dilation (AAD) by echocardiography. Brain natriuretic peptide (BNP) is a hormone secreted by the heart. In dysfunctional treated hypertensives, it is known that BNP is increased in patients with hypertensive disease. Although not expectable in hypertensive patients at first glance, the increase in BNP is actually increased in patients with hypertension.

**Methods:** The MEHLP study is a screening study aimed to evaluate the amount of cardiovascular subclinical pathology in an asymptomatic general population. To this aim the population ~45 years (1474 people, 61±14 years, m=397, males 48%, left ventricular ejection fraction 58±5%, cardiac mass index 118±42 mg/m²) from the community of Montignoso, Massa, Italy, was screened with biohumoral evaluation comprehensive of NT-proBNP, CCS assess by thoracic CT, IMT and AAD (the latter in 850subjects) by echography.

**Results:** Diabetes, hypertension and hypercholesterolemia were present in 11%, 41% and 38% of subjects, respectively; 13% were actual smokers, 31% past smokers. Median NT-proBNP was 59 ng/L (Q range 33-101), CCS, IMT (bilateral sum) and AAD were, respectively, 156±521 U.A. 1.6±0.3 mm and 32.4±4 mm, with 11%, 15% and 4% of people showing CCS, IMT and AAD respectively higher than 400 U.A., 2 mm and 40 mm. CCS > 400 U.A., IMT > 2 mm and AAD > 40 mm were all predicted at ROC analysis by plasma NT-proBNP levels (AUCs 0.589, 0.591, 0.596 respectively, p<0.05 for all). NT-proBNP was higher in patients with a) CCS > 400 U.A. (64, 42-128 vs. 57, 32-98 ng/L, p<0.01), b) IMT > 2 mm (72, 38-139 vs 58, 32-95, p<0.01), c) AAD > 40 mm (65, 36-171 vs 59, 33-99, p<0.05), despite no differences in left ventricular ejection fraction, nor in cardiac mass; this findings were confirmed in the subset of hypertensives, while not in subject with diabetes, hypercholesterolemia, or with past/present smoking habit.

**Conclusions:** NT-proBNP level, within the upper normal range, predicts subclinical coronary atherosclerosis and vascular health, namely in asymptomatic hypertensive subjects, with no relation with heart structural and functional involvement, possibly reflecting a vascular source of production and secretion.

**Selective serotonin reuptake inhibitors exert a negative effect on peripheral wave reflections**

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**Purpose:** In view of the high likelihood that hypertensives will have comorbid anxiety and depression, all hypertensives should be screened for concurrent psychiatric illnesses and treatment. We hypothesized that there is a relationship between the administration of selective serotonin reuptake inhibitors (SSRIs) and arterial stiffness, a hallmark of the cardiovascular aging process.

**Methods:** We studied 210 consecutive untreated stage I/II essential hypertensive subjects (aged=62±9 years, 110 female, office blood pressure (BP) = 163±91 mm Hg). The participants were divided into group A (n=83), those receiving SSRIs and group B (n=127), those without taking any antidepressant therapy. Arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (c-f PWV) by means of a computerized method (Complior SP). Venous blood sampling was performed for the estimation of routine metabolic profile.

**Results:** The two groups did not differ regarding age, gender, office systolic/diastolic BP as well as serum glucose and triglycerides levels (93±9 vs 84±9 mg/dl and 128±8 vs 119±9 mg/dl, respectively, p=NS in all cases). Group A was characterized by increased levels of body mass index (32.4±3 vs 29.2±4 kg/m², p=0.015) and elevated cholesterol plasma levels compared to group B (231±32 vs 220±36 mg/dl, p=0.05). Group A compared to group B exhibited significantly increased c-f PWV (8.4±0.3 vs 7.2±0.5 m/sec, p=0.02) and this difference remained significant after adjustment for confounders (p=0.03). In the SSRIs treated-hypertensives, c-f PWV was correlated with age (r=0.35, p=0.015) and office systolic BP (r=0.33, p=0.02), while no significant correlation was demonstrated with cholesterol levels (p=NS).

**Conclusions:** The administration of SSRIs exerts an incremental effect on arterial stiffness, thus accelerating the vascular aging process.

**Renin-angiotensin aldosterone system gene polymorphisms and their association with vascular impairment in patients with essential hypertension**

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**Purpose:** The angiotensinogen (M235T) and aldosterone synthase (CYP11B2) gene polymorphisms have been positively associated with vascular properties. Therefore, in the present study we examined whether these variants affect carotid-femoral pulse wave velocity (c-f PWV), flow mediated dilation (FMD), ultrasound measurement of the intima-media thickness of carotid arteries (C-IMT), augmentation index, ankle-brachial index.

**Methods:** The study population consisted of 318 untreated essential hypertensives and a control group, consisted of 193 matched subjects. c-f PWV, FMD, ultrasound measurement of the C-IMT, augmentation index and ankle-brachial index were evaluated. The gene mutations frequencies were determined using polymerase chain reaction (PCR) technique. Serum cystatin C levels and inflammatory biomarkers were measured by the ELISA method.

**Results:** TT homozygotes had significantly lower FMD compared with M al- leles carriers in controls (p=0.035, p<0.015) and office systolic BP (r=0.33, p=0.02), while no significant correlation was demonstrated with cholesterol levels (p=NS).

**Conclusions:** The administration of SSRIs exerts an incremental effect on arterial stiffness, thus accelerating the vascular aging process.
similar results were obtained for hypertensives, though without reaching statistical significance (p=0.07). Moreover, after adjustment for co-variables, cystatin-C levels correlated significantly with PWV values both in total (r=0.27, p=0.03) and in hypertensive populations (r=0.23, p=0.008). Interestingly, in univariable analyses, increased levels of cystatin-C (above 75th percentile) correlated with higher PWV values (p=0.0019).

Conclusions: We have shown that TT homozygotes had significantly lower FMD in controls and c-PPW was higher in TT homozygotes compared with MM+MT genotypes in hypertensive patients. In addition, we have observed higher values of IMT in 344TT homozygosity, in the group of hypertensives, while T allele carriage was significantly associated with higher prevalence of atherosclerotic plaques in the study population. Our results suggest that angiotensinogen genotypes are associated with arterial stiffness, whereas CYP11B2 promoter variant potentially constitutes a marker of subclinical atherosclerosis in untreated hypertension.

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Insulin resistance is associated with increased large artery stiffness in normotensive healthy adults

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Aim: At present there is limited evidence on the relationship between insulin resistance (IR) and measures of large artery stiffness (AS) and wave reflections in normotensive healthy adults. Aim of the present study was to explore this issue in 90 normotensive (Systolic) blood pressure (BP), 107.1±9.3; diastolic (D) BP 69.6±7.7 (mmHg), normoglycemic, non-obese, otherwise healthy adults (mean age 48.1±10 yrs, 50% female).

Methods: IR was assessed by HOMA index and subjects were classified into IR tertiles, based on the distribution of HOMA index values. Recordings of pulse wave waveform were obtained by means of a previously validated oscillometric device for ambulatory BP monitoring with in-built transfer-function like method. Aortic pulse wave velocity (PWV, m/s) and other measures derived from pulse wave analysis such as augmentation index (%), central SBP (cSBP), central PP (cPP), central DBP (cDBP) and central pulse pressure (cPP) were computed. Peripheral SBP and DBP and heart rate (HR) were recorded and pulse pressure (PP) calculated as the difference between SBP and DBP.

Results: After multiple regression analysis adjusting for age, sex, HR and BMI, there was a significant overall effect of IR on measures of large artery stiffness and in central and peripheral BP levels. IR was associated with increased aortic PWV, and with higher central and peripheral SBP and DBP levels. See table.

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MODERN CARDIAC REHABILITATION MOVING BEYOND FUNDAMENTALS

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Multidisciplinary cardiac rehabilitation and survival in The Netherlands

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Purpose: This study assessed the effects of multidisciplinary cardiac rehabilitation (CR) on survival in a large cohort of patients with coronary artery disease in The Netherlands.

Methods: The cohort consisted of persons insured with Achmea, a health insurance company in the Netherlands covering approx. 20% of the Dutch population (3.3 million insured persons). All patients with an acute coronary syndrome (ACS) with or without ST elevation and patients that underwent coronary revascularization in the period 2007-2010, based on insurance claims, were included. Patients were categorized as having received CR when an insurance claim for CR was made within the first 180 days after the cardiac event or revascularisation. Propensity score weighting was used to control for confounding by indication.

Results: A total of 35,919 patients were analyzed, of which 11,014 (30.7%) used CR. Median follow-up time after CR was 19.3 months (min. 0 months, max. 42 months). Crude mortality rates during the study period were 2.6% (287 patients) for CR users and 8.7% (2,160 patients) for nonusers (adj. HR 0.68, p=0.001). The table shows mortality rates among different patient categories. There was a non-significant difference (p=0.14) in survival between CR users receiving physical therapy (adj. HR 0.62) and CR users not receiving physical therapy (adj. HR 0.74).

Mortality rates in CR users and non-user

<table>
<thead>
<tr>
<th>Patient category</th>
<th>Crude mortality rates (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG surgery</td>
<td>6.3</td>
<td>6.8 (4.7-9.8)</td>
</tr>
<tr>
<td>PCI</td>
<td>53.9</td>
<td>6.3 (5.0-7.7)</td>
</tr>
<tr>
<td>PCI elective</td>
<td>25.6</td>
<td>5.8 (5.1-6.5)</td>
</tr>
<tr>
<td>ACS with ST elevation</td>
<td>54.3</td>
<td>10.6 (8.4-13.2)</td>
</tr>
<tr>
<td>ACS without ST elevation</td>
<td>20.5</td>
<td>9.2 (7.7-11.2)</td>
</tr>
<tr>
<td>Total</td>
<td>30.7</td>
<td>8.7 (6.6-11.2)</td>
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</tbody>
</table>

Conclusion: While patients with an acute coronary syndrome and/or coronary revascularization in The Netherlands, the use of multidisciplinary CR was associated with a survival benefit of 32%.

Cardiovascular rehabilitation after a first acute coronary syndrome and the risk of recurrence and death in patients from the French MONICA registries

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Purpose: Cardiovascular rehabilitation following the occurrence of an acute coronary event (ACE) is more and more commonly used over the past years. However, differences still remain in prescription rates, depending on age, gender or the severity of the event. The aim of this work was to assess the prognostic influence of rehabilitation after ACS in the current medical practice.

Methods: Our study was based on 2008 data from the French MONICA population-based registry which collects all cases of ACS occurring in people aged 35-74 in 3 French areas located in North, North-Eastern and South-Western France. The population consisted of 1869 consecutive hospitalized ACS, after exclusion of those who died in the first 28 days of follow-up. The relationship between prescription of cardiovascular rehabilitation and composite outcome (ACS- recurrence or death) was analyzed using Cox models adjusted for living area, age, number of diseased vessels, diabetes, cardiovascular treatments and delays between symptoms and the first medical care.

Results: There were 171 ACS-recurrences or deaths during a median follow-up of 18.1 months. The population consisted of 23.6% of women. The rate of cardiac rehabilitation was significantly higher in men than in women (36% vs. 26%, p=0.0001) and decreased with age. After multivariate adjustment the risk of composite outcome occurrence was identical in men and women for STEMI but higher in women for UA/NSTEMI [adjusted HR 1.75, 95% confidence interval (1.10 to 2.77)]. Rehabilitation was associated with a decrease of ACS-recurrences and deaths whatever the definition of ACS (global adjusted HR 0.48, 0.32 to 0.73). However a significant interaction between rehabilitation and gender has been found in UA/NSTEMI (p=0.04) but not in STEMI. A stratified analysis for gender in UANSTEMI showed a significant benefit of rehabilitation in women (adjusted HR 0.66, 0.01 to 0.44) but not in men [adjusted HR 0.82, (0.39 to 1.72)].

Conclusions: Whatever the definition of ACS, cardiovascular rehabilitation was associated with a reduction of ACS-recurrence and death, and benefits both sexes. However rehabilitation seems to be more beneficial in women presenting UA/NSTEMI in whom rehabilitation is less prescribed and in whom the rate of recurrence and death is higher.
Phase II comprehensive cardiac rehabilitation prevents readmission for heart failure in patients with chronic heart failure and high brain natriuretic peptide levels

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Purpose: The purpose of this study was to investigate the effects of phase II comprehensive cardiac rehabilitation (CR) in patients with chronic heart failure (CHF) and high brain natriuretic peptide (BNP) levels.

Methods: We studied 312 patients with CHF (215 males; age 71±10 years) who were hospitalized for acute decompensated heart failure. Patients were classified into four groups according to BNP levels at the time of discharge and participation in phase II CR. The CR with low BNP group (n = 67) included patients who participated in CR and had BNP levels less than 200 pg/mL, the CR with high BNP group (n = 74) included patients who participated in CR and had BNP levels more than 200 pg/mL, the non-CR with low BNP group (n = 64) included patients who did not participate in CR and had BNP levels less than 200 pg/mL, and the non-CR with high BNP group (n = 104) included patients who did not participate in CR and had BNP levels more than 200 pg/mL. Readmission for heart failure was defined as a patient readmitted to the hospital because of heart failure during a follow-up period of up to 10 years.

Results: Multivariate Cox proportional analysis showed that participation in phase II CR was a significant predictor for readmission of heart failure (adjusted hazard ratio, 0.66; p<0.001). There were no significant differences between the two groups regarding compliance to pharmaceutical therapy. Follow-up data was available in 227 (94%) patients, with a mean follow-up time of 25.7 months. Composite endpoints were found in 23 (10%) patients and tended to be more frequent in non-CG (17% vs 9%; p=0.182). With Cox regression analysis, non-compliance behavior was associated with a higher likelihood of composite endpoint occurrence, although no statistical significance was achieved (HR:2.2, 95% CI:0.7-6.4).

Conclusion: CRP compliant patients have a significant higher improvement in cardiovascular risk profile, functional capacity and tend to suffer less cardiovascular events than non compliant patients.

The effects of respiratory muscle trainings on systemic inflammation and fibrosis process in patients with heart failure


Background: Number of studies showed the effectiveness of Respiratory Muscle trainings (RMT) as a part of comprehensive cardiac rehabilitation (CR). The mechanisms of their positive effects in cardiac patients are still not well known.

Purpose: To study the relations of long-term effects of RMT started in patients with NYHA III-IV-class heart failure (HF), with the intensity of systemic inflammation and pulmonocardiac fibrosis.

Methods: 61 patients 64±5.2 years old with NYHA III-IV HF were randomized to either an exercise training group (EG) (30pts) or to a control group. The CG patients had standard CR according to the national guidelines. The EG participated additionally in a RMT with gradual increase of inspir and expire resistance. 12-15 RMT were held at the hospital with following continuation at home for 12 months by patients themselves. Trainings were held for 20-30 minutes 1-2 times every day. Plasmatic levels of C-reactive protein (CRP), aldosterone and the carboxyterminal propeptide of human type I procollagen (PICH) were studied at discharge point and in 12 months.

Results: In 12 months peak VO2 increased significantly in EG (11.58±2.54 ml/kg/min in EG vs 9.17±2.12 ml/kg/min in CG, p<0.05). EG patients showed significant decrease in CRP level (5.2±2.4 mg/dl in EG vs 8.1±2.1 mg/dl in CG, p<0.05), aldosterone level (60.5±9.9 pg/ml in EG vs 151.6±18.3 pg/ml in CG, p<0.05), PICH (67.5±7.8 mg/ml in EG vs 104.6±11.2 mg/ml in CG, p<0.05). RMT helped to stabilize mean pulmonary pressure (33.5±4.7 mm Hg in EG vs 44.2±7.6 mm Hg in CG, p<0.05). Health related quality of life measured by SF-36 increased in both groups, but results in physical functioning, bodily pain, vitality, role emotional scales were significantly higher in EG patients.

Conclusion: RMT in patients with HF are effective in decreasing the level of systemic inflammation, neurohumoral activation and collagen synthesis and thus regarding fibrosis, besides improving physical capacity, stabilizing pulmonary pressure and increasing health-related quality of life.

Compliance to a cardiac rehabilitation program: what benefits and prognosis impact?


Background: Cardiac rehabilitation programs (CRP) have consistently demonstrated the ability to improve cardiac risk factors and reduce morbimortality. Thus, compliance to CRP is an essential requirement to achieve the goals of secondary cardiovascular prevention.

Objective: To assess the clinical benefits and CRP compliance impact on prognosis in a coronary heart disease population.

Methods: We evaluated a total of 241 patients referenced to a CRP after an acute coronary syndrome (ACS), recruited between September 2008 and November 2010. Information on socio-demographic, clinical and functional data was collected pre and post CRP. Functional capacity was assessed in metabolic equivalent (METs), determined by exercise stress testing. Telephonic interview to patients with at least 12 months of follow-up after index event was performed to assess the occurrence of composite endpoint of overall mortality and nonfatal cardiovascular events.

Results: Study population consisted of 241 patients, mostly male (89%), aged 54±10 years (range 28-80). Non compliance was found in 24 (10%) patients and it was more common in women than men (23% vs 8%; p=0.030) and in obese patients (18% vs 8%; p=0.024). Significant differences were found in other base-line characteristics, including ACS type and severity indicators. At 6 to 12 months post index event, health status comparison between the 2 groups demonstrated that compliers achieved better control of cardiovascular risk profile: higher smoking cessation rate (70% vs 18%, p=0.001) and higher rates of adequate physical activity (≥600 METS/minute/week) [82% vs 25%, p=0.022]. A significant improvement was found, only in the compliant group (CG), regarding functional capacity [-0.8 (1.6) METS, p<0.001] and lipid profile (LDL-cholesterol: -39.1 [38.9, 6.0], p<0.001; HDL-cholesterol: +3.2 [8.7], p<0.001 and triglycerides: -38.7 [102.7], p<0.001). There were no significant differences between the two groups regarding compliance to pharmaceutical therapy. Follow-up data was available in 227 (94%) patients, with a mean follow-up time of 25.7 months. Composite endpoints were found in 23 (10%) patients and tended to be more frequent in non-CG (17% vs 9%; p=0.182). With Cox regression analysis, non-compliance behavior was associated with a higher likelihood of composite endpoint occurrence, although no statistical significance was achieved (HR:2.2, 95% CI:0.7-6.4).

Conclusion: CRP compliant patients have a significant higher improvement in cardiovascular risk profile, functional capacity and tend to suffer less cardiovascular events than non compliant patients.

Beneficial effects of rehabilitation in comparison with resynchronization therapy in patients with NYHA III heart failure

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Background: Indications to cardiac resynchronization therapy (CRT) have been extended in 2010. However, there is large group of patients with ejection fraction -35%, severe heart failure (HF) and QRS -120ms, who are not qualified to CRT. They are treated with optimal pharmacotherapy. We compared outcomes of rehabilitation of patients in NYHA III heart failure and patients with implanted CRTD device without rehabilitation.

Methods: The study included 47 patients with NYHA III HF and EF -35% on optimal pharmacotherapy.

Table 1. Comparison of clinical outcomes of patients with and without rehabilitation
mal pharmacotherapy. The etiology of HF was comparable in both groups. 27 patients with QRS >120 ms had CRT-D implanted and 20 patients with QRS >120 ms had ICD implantation and went through the training program (aerobic exercises on ergometer, 3 times a week for 3 months). All patients were optimally treated pharmacologically. They had echocardiography and cardipulmonary exercise test (CPX) performed at baseline and after 6 months.

Results: All results are presented in Table 1.

Conclusions: Patients with NYHA III heart failure have better outcomes when compared with CRT group. Rehabilitation is a noteworthy therapeutic option for patients with severe heart failure and no indications to CRT.

NOVEL APPROACHES TO EXERCISE TRAINING

3804 Biventricular filling impairment limits cardiac performance during exercise in healthy subjects

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Background: Constraints in current imaging techniques have resulted in considerable disagreement as to what constitutes normal changes in left and right ventricular (LV, RV) volumes during exercise. The aim of this study was to determine whether biventricular end-diastolic and end-systolic volumes (EDV and ESV) using a novel CMR methodology during strenuous exercise.

Methods: Twenty-two healthy and physically active subjects (19 male, 3 female, age 32 ± 7 years) underwent CMR at rest and during supine exercise on a programmable cycle ergometer. Biventricular volumes were obtained at rest (heart rate 63 ± 11 bpm) and whilst cycling at moderate (15 ± 16 bpm) and strenuous (155 ± 11) bpm workload intensities. Images were acquired during exercise and free-breathing (12-15 contiguous 8mm slices) using an un gated real-time CMR sequence. We developed software to enable retrospective synchronization of long and short-axis images with compensation for respiratory phase translation. Thus, endocardial borders could be delineated in a bi-plane model.

Results: There was significant inter-observer agreement for all volume estimations (eg. intra-class correlation coefficients r=0.97 and n=0.98 for EDV and CO respectively, p<0.001). Biventricular cardiac output (CO) increased by 11.1 ± 51% from rest to moderate exercise (7.7 ± 4.1 vs. 16.3 ± 4.8 l/min; p<0.001) and by a further 30.8 ± 16% to strenuous exercise (16.3 ± 4.8 vs. 21.1 ± 5.3 l/min; p<0.001). The total 174 ± 60% increase in CO was due to a 146 ± 23% increase in HR and a 9.1 ± 13% increase in stroke volume (SV).

Interestingly, SV increased during moderate exercise (124.2 ± 141.3 ml; p<0.001) but then decreased during strenuous exercise (141.3 ± 135.3 ml; p=0.002). The early increase in SV was due to augmentation of both systolic function (end-systolic volume (ESV) -15 ± 11%, p<0.0001) and diastolic filling (end-diastolic volume (EDV) +23 ± 7%, p<0.02). Although during strenuous exercise there was further augmentation of systolic function (ESV -20 ± 16%, p<0.0001) and LV end-diastolic filling was maintained (EDV -10 ± 7%; p<0.0001). This reduction in EDV during strenuous exercise occurred in all subjects and was greater for the RV than for the LV (12 ± 8 vs. -7.5 ± 5%, p<0.03).

All other changes in cardiac volumes were similar for LV and RV (p<0.05).

Conclusions: A novel CMR methodology of biventricular volume assessment was used to demonstrate augmentation of biventricular filling and ejection during moderate exercise in healthy subjects. However, at higher exercise intensities, diastolic filling is compromised and attenuates further stroke volume increases.

3805 Evaluation of a newly designed shirt-based ECG and breathing sensor for home based training as part of cardiac rehabilitation for coronary artery disease

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Background: The advantages of a structured cardiac rehabilitation (CR) program are well known. However, participation in phase III CR is low. This problem could be overcome by implementing a home-based supervised CR, but new technology is needed to allow that supervision and improve adherence to CR.

The novel tool (HeartCycle’s GEx-System) is intended as a closed-loop cardiovascular disease management tool with support for both the professional and the patient, focused on CR based on physical exercise. The patient side system comprises a wireless sensor attached to a shirt that senses vital parameters such as respiration and ECG. All information and activity data were downloaded to a PDA which gives feedback and guidance to the patient during the exercise.

Methods: A phase I study was performed to evaluate feasibility and function of the GEx-System devices for home-based CR used during actual physical exercise. 50 patients were included during CR 36 ± 13 days after intervention (7 women, age: 69 ± 9 years, BMI: 26 ± 3, EF: 58 ± 10%) for different cardiac reasons (valve replacement: n=9, Mit: n=29, CABG: n=25, others n=2). A standard exercise test (25 Watt/min) was performed. ECG, hart rate, breathing rate were monitored using standard equipment and GEx-device simultaneously. The heart rate was also reported to the patients on the PDA.

Results: Mean exercise performance was 90 ± 32 Watts with a VO2peak of 13.4 ± 4 ml/min/kg. There was an excellent correlation between heart rate measured by the GEx-device and standard 12-lead ECG (r=0.97). All occurring arrhythmia were detectable (e.g. atrial fibrillation, ventricular ectopic beat). Breathing frequency during exercise was evenly well correlated (r=0.74). Additional heart rate measurement with PDA also exhibited an excellent correlation for heart rate for training (r=0.97).

Conclusions: There was an excellent correlation between standard spirometry and the GEx-device measuring of heart rate, breathing rate and detection of arrhythmias. As this sensor in combination with a special shirt is easy to use and wear, it seems suitable for monitoring home-based CR. Further studies are needed to evaluate applied training prescriptions.

3806 Music as additional therapeutic option to exercise training for endothelial dysfunction in patients with stable coronary artery disease

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Purpose: To evaluate the effects of listening to favorite music added to regular exercise training on the endothelial function, assess through changes of circulating blood markers of endothelial function: the stable end products of nitric oxide metabolism (nitrites - nitrates) and reactive oxygen species (RSNO) generated by reduced nicotinic oxide, in examined patients with stable coronary artery disease (CAD).

Methods: 65 pts with stable CAD were studied. At baseline and 3 weeks later, in all pts values of NOx and RSNO were evaluated and exercise test was performed. After the initial study, pts were randomized to trained (T, n=20) and non-trained (NT, n=20) groups. Patients in T and MT groups underwent a supervised 3 weeks aerobic exercise training at residential center, while non-trained group received usual community care. Additionally to exercise training, patients in MT group were listening their favorite music for half an hour every day. To elucidate the dynamic of nitric oxide metabolism in the circulation, NOx and RSNO concentration were determined according to the modified Saville-Griess method.

Results: Baseline values of NOx and RSNO were similar in T, MT and NT group. After 3 weeks NOx increased significantly in T group (from 31.5 ± 9.5 to 42.0 ± 11.0 μmol/l, P<0.005), as well as in MT group (from 32.7 ± 9.0 to 49.0 ± 10.5 μmol/l, P<0.001) and those values were significantly higher than in NT group (P<0.05 and P<0.001). After 3 weeks value of NOx was significantly higher in MT than in T group (P<0.05). In all groups, value of RSNO increased after 3 weeks: in T group from 3.0 ± 1.5 to 4.4 ± 1.3 μmol/l (P<0.005), in MT from 3.2 ± 1.3 to 5.3 ± 1.3 μmol/l (P<0.001) and in NT group from 2.8 ± 1.1 to 5.1 ± 1.4 μmol/l (P<0.005). Different rate of increased RSNO in examined groups resulted in significantly higher RSNO in MT than in T group (P<0.05). In all groups, value of RSNO increased after 3 weeks: in T group from 3.0 ± 1.5 to 4.4 ± 1.3 μmol/l (P<0.005), in MT from 3.2 ± 1.3 to 5.3 ± 1.3 μmol/l (P<0.001) and in NT group from 2.8 ± 1.1 to 5.1 ± 1.4 μmol/l (P<0.005). Change of exercise test at baseline were similar in T, MT and NT. After 3 weeks exercise capacity significantly increased in T and MT group (P=0.001 both), however increase in exercise capacity was higher in T than in MT group (45% vs 27%).

Conclusion: In pts with stable CAD listening to favorite music in addition to regular exercise training and standard therapy, leads to more pronounced improvement in endothelial function, expressed through higher increased of NOx and RSNO, than exercise training alone. These improvement in endothelial function is associated with significant improvement in exercise capacity.

3807 Exercise capacity in patients with coronary artery disease: what is beyond global left ventricular systolic function?


Purpose: Exercise capacity is influenced by many factors and elucidating the mechanisms for cardiac-related exercise limitation has been technically difficult. In this study we sought to determine the effect of cardiac function on exercise capacity.

Methods: Prospective study including patients admitted to an outpatient cardiac rehabilitation program (CRP) after suffering an acute coronary event between January 2011 and September 2011. Echocardiography data and exercise capacity were evaluated at the beginning and at the end of the CRP. All echocardiographic measurements and activity dummying according to current guidelines and exercise capacity assessed by estimated metabolic equivalents (METs) achieved on exercise stress testing.

Results: Forty-five patients were evaluated, 38 (84%) male, mean age of 54 (±9
Passive whole-body exercise training with periodic acceleration improves endothelial function in sedentary subjects

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Introduction: Periodic acceleration in the direction of the spinal axis through repetitive movements increases shear stress to the vascular endothelium. Thus, we assessed the hypothesis that whole-body periodic acceleration with a new “passive exercise” device would enhance release of nitric oxide (NO) into the circulation and endothelial function in sedentary adults.

Methods: We enrolled twenty sedentary subjects (42 ± 4 years; 12 women, 8 men) not taking any medication. Each subject was randomly assigned to remain sedentary or perform exercise training for 4 weeks, followed by cross-over. Periodic acceleration was applied with a horizontal motion platform (AT101; Non-invasive Monitoring Systems) at a frequency of 2-3 Hz and approximately ± 0.25 g for 45 min. Venous blood was sampled before and immediately after the first and 20th sessions. The amount of plasma NO end-products (nitrate plus nitrite) was measured by the Griess reaction. Increases in right brachial artery diameter were examined at rest, during reactive hyperemia (flow-mediated dilatation: %FMD) and after sublingual administration of 0.3 mg of nitroglycerin (%NTG) using high-resolution ultrasound, measurements of which were repeated at baseline and after the 20th session.

Results: All subjects completed the study with no adverse side effects. There were no significant changes in resting heart rate and arterial pressure, body weight, or lipid profiles after periods with and without exercise. Periodic acceleration significantly increased plasma levels of NO end-products from 17 ± 5 µM at baseline to 24 ± 9 µM after the completion of 20 sessions (p < 0.05), while those who were not resistant.

Conclusions: Whole-body exercise training with periodic acceleration improves vascular endothelial function through an increase in NO release in sedentary adults. This device may offer an alternative for exercise patients with medical conditions limiting physical activity.

3809 Exercise echocardiography - effects of endurance training and ageing

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Purpose: To study the effects of endurance training and ageing on echocardiographic measures of myocardial function at rest and during exercise.

Methods: Four groups of healthy, normal weight males; master athletes (running over 60% of maximum workload), young athletes with similar level of physical activity, and sedentary age-matched controls underwent exercise test determining VO2peak, and echocardiography at rest and during supine bicycle exercise test at 60% of maximum workload. Linear regressions were performed to simultaneously assess the effects of training (two groups) and age (continuous) on echocardiographic measures.

Results: VO2peak differed considerably between young and old and between athletes and non-athletes. Dimensions of left atrium and ventricle as well as transmitral flow patterns at rest were affected by both training and age. See table. Effects of age were also found on systolic and diastolic tissue-Doppler measures both at rest and during exercise.

Conclusion: This study finds more effects of ageing than endurance training on measures of myocardial function. The effects of training are not found during exercise.

3810 OPTIMISATION OF MYOCARDIAL REPERFUSION IN STEMI

Sustainable TGF beta receptors are associated with infarct size and ventricular dysfunction in S1-elevation myocardial infarction

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Objectives: The aim of the study was to investigate circulating markers of apoptosis in relation to infarct size, left ventricular dysfunction and remodeling in an STE-levation myocardial infarction (STEMI) population undergoing primary percutaneous coronary intervention (PCI).

Background: Immediate re-opening of the acutely occluded infarct-related artery via primary PCI is the treatment of choice in STEMI to limit ischemia injury. However, the sudden re-infection of blood flow can lead to a local acute inflammatory response with further endothelial and myocardial damage, so-called reperfusion injury. Apoptosis is suggested to be a key event in ischemia-reperfusion injury, resulting in LV-dysfunction, remodeling and heart failure.

Methods: We included 48 patients with STEMI undergoing primary PCI. Blood samples were collected prior to PCI and after 24 hours. Plasma was separated for later analysis of soluble tumor necrosis factor receptor (sTNFR) 1, sTNFR2, sFas and sFas ligand (sFasL) by ELISA. Infarct size, left ventricular (LV) function and remodeling were assessed by cardiac magnetic resonance imaging at 4 days and 4 months after STEMI.

Results: The levels of sTNFR1 at 24 h as well as the relative increases in sTNFR1 and sTNFR2 over 24 h showed consistent and significant correlations with infarct size and LV-dysfunction four months after STEMI. Moreover, both sTNFRs correlated with apoplosis markers correlated significantly with measures of remodeling.

Conclusion: In STEMI patients, circulating levels of sTNFR1 and sTNFR2 are associated with infarct size and LV dysfunction. This provides further evidence for the role of apoptosis in ischemia-reperfusion injury.

3815 Hemostatic and fibrinolytic profile in patients with ST-segment elevation myocardial infarction resistant to fibrinolysis


Despite primary PCI is the treatment of first choice in patients with ST-segment elevation myocardial infarction (STEMI), for accessibility reasons, the fibrinolyis continues being the first line treatment about 30-70% of these patients, however in 40% of them is ineffective for unknown reasons.

Aim: To analyze whether there exists some association between hemostatic and fibrinolytic factors determined in circulating plasma and if it correlates with the tenents into the coronary thoroms, in patients resistant to fibrinolysis compared to those who were not resistant.

Methods and Results: 20 patients (age 57±13y; 10 female) who underwent PCI
for a first STEMI with initial TIMI 0 flow were included. Of these, 10 underwent primary PCI (group A) and the other 10 were subjected to rescue PCI (group B) because of ineffective fibrinolysis (TTK). In all patients tissue factor activity (TFa), TF Ag and tissue factor pathway inhibitor (TFPI), von Willebrand factor (VWF), D-dimer, plasmin inhibitor activated (PAI-1) and tissue plasmin activator (t-PA) were determined. The coronary thrombus was obtained during PCI by aspiration catheter in all patients. Specimens were submitted to immunohistochemical analysis. In order to know if all patients underwent primary PCI a thrombus sensitive to lysis, thrombus formation by thrombin was induced “in vitro”, and an effective thrombolysis by r-TPA was observed in 100% of patients.

There were no differences between both groups in terms of age, sex, car- diovascular factors, time symptoms onset to balloon, infarct localization and number of affected vessels. Patients who underwent rescue PCI showed a higher D-dimer plasma level regarding patients who underwent primary PCI (2234.3±706.5 vs 774.5±1339.8 ng/ml, p<0.03). In plasma, D-dimer levels were associated to TFa (R=0.95, p<0.01) and FVW levels (R=0.65, p<0.04). In the thrombus, FVW plasma levels were correlated with PAI-1 (R=0.79, p<0.006), CD34 (R=0.85, p<0.004) and P-selection (R=0.77, p=0.002). However, in patients who underwent primary PCI, D-dimer levels were associated with 1-TPI (R=0.94, p<0.001) and FVW levels were inversely associated with TFPI (R=0.87, p<0.01) in plasma. In addition, in the thrombus the content of fibrin was associated with CD34 and FVW (R=0.71, p=0.03; R=0.73, p=0.02, respectively).

Conclusion: There are clearly different characteristics of thrombotic and fibrinolytic fac- tors. Resistant patients to fibrinolysis show positive correlations between strongly thrombotic factors, while in no resistant patients to fibrinolysis there are a trend to haemostasis between prothrombin and fibrinolytic factors.

### Long term effect of minimising pain-to-balloon time on mortality in ST-elevation infarction. The ANIN Myocardial Infarction Registry

**Objectives:** To determine the safety and efficacy of selective thrombus aspiration in patients with ST elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI) at a high volume centre.

**Methods:** In a prospective “all-comer” registry clinical and procedural characteristics, PBT and 9-year mortality were determined in consecutive STEMI pts treated with pPCI in our tertiary centre between Feb 2001 and Oct 2002. We divided pts according to PBT into three groups: A) <180, B) 180-360 and C) >360 minutes.

**Results:** Among 1064 consecutive STEMI pts treated with pPCI, PBT and mor- tality were known in 937 (94%) pts. There were 350, 461, 196 pts in group A, B, C, respectively. Pts in group A compared to B and C were younger, more often were male and smokers, less frequently had history of CAD, more frequently had diabetes, hypertension, Killip class, and the prevalence of hypertension, Killip class, and the frequency of MI and RT did not differ between our institution and the national data.

**Conclusion:** If our findings are confirmed in larger studies, the current guidelines may have to be revised regarding the importance of LBBB chronically.

### 3817 Left bundle branch block and suspected myocardial infarction: an under-treated patient group?

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**Purpose:** According to ESC guidelines, a new or presumed new left bundle branch block (LBBB) in patients with suspected myocardial infarction (MI) constitutes an indication for acute reperfusion treatment (RT). Our aim was to investigate if this group of patients was treated according to guidelines as well as comparing them with patients having a previously known LBBB (oLBBB). **Methods:** Retrospective collection of data from the Swedeheart registry for pa- tients with LBBB and suspected MI, admitted to the CCU at Örebro University Hospital during 2009 and 2010. All data was checked against medical records. The definition of LBBB, MI and RT follows Swedeheart registry criteria. We di- vided the patients in two age groups: <80 or ≥80 years and analyzed LBBB chronicity (oLBBB or eLBBB), diagnosis of MI and prevalence of RT. Regarding frequency of MI and RT, we compared our data with the entire national Swede- heart database for 2009 (3001 patients with LBBB). For statistical calculation we used Fisher’s exact test and SigmaStat v3.5 software.

**Results:** A diagnosis of MI was significantly more common in the group ≥80 years compared to <80 years (53.8% vs 24.5%, p<0.006). The prevalence of MI was similar in the groups mLBBB and eLBBB (33% resp 36%, p=0.946). RT was significantly more often administered to patients with mLBBB compared to eLBBB (41.6% vs 7.8%, p<0.001), and the difference was even more pronounced in the age group <80 years. Frequency of MI and RT did not differ between our institution and the national data.

**Conclusions:** We found no correlation between LBBB chronicity and incidence of myocardial infarction. The frequency of RT is low, but somewhat higher in the group <80 years. In this age group, a new LBBB identified only half of the patients with a final diagnosis of MI, which means that strict adherence to reperfusion guidelines may leave half of the patients untreated.

If our findings are confirmed in larger studies, the current guidelines may have to be revised regarding the importance of LBBB chronically.
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Drug eluting stents are associated with lower MACE rates compared to bare metal stents in small coronary arteries treated by primary PCI for STEMI

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Purpose: Drug eluting stent (DES) implantation has been shown to improve outcomes in primary PCI for STEMI, although there is limited data about their use in small coronary arteries. We aimed to compare medium-term outcomes of patients with small coronary arteries with DES versus BMS placement for primary PCI for STEMI.

Methods: 2170 consecutive patients underwent primary PCI for STEMI at a single high-volume centre between October 2003 and September 2010. Of these, 863 had culprit arteries with reference vessel diameter <3mm, which were defined as small coronary arteries. The primary end point was major adverse cardiac events (MACE), defined as death, myocardial infarction (MI), stroke and target vessel revascularization (TVR). Median follow-up was 2.0 years (IQR 0.7-3.6 years).

Results: 246 patients underwent PCI with DES and 637 with BMS. Patients undergoing DES implantation were older, more likely to be diabetic and more likely to have undergone previous PCI. Kaplan-Meier estimates (Figure 1) of medium-term MACE demonstrated a significant difference in favour of DES (21.1% vs. 16.4%, p=0.04). Age-adjusted Cox analysis demonstrated this benefit to be maintained with nongraft adjacencies, (hazard ratio 0.70 [95% CI 0.49-0.97]). In addition, this difference persisted after regression adjustment incorporating a propensity score (age, stent length, stent width, gender, ethnicity, previous MI, PCI or coronary artery bypass grafting, diabetes, hypertension, hypercholesterolaemia, smoking status, presence or absence of shock, and ejection fraction) into the hazards model as a covariate (hazard ratio 0.82 [95% CI 0.47-0.96]).

Conclusions: In patients with small coronary arteries, DES implantation appears to be associated with lower MACE rates than BMS implantation in primary PCI for STEMI.

IMPORTANCE OF CO-MORBIDITIES IN HEART FAILURE

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Prognostic impact of the timing/degree of Acute Kidney Injury and Acute Heart Failure: an evaluation of the RIFLE Criteria

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Background: Various studies have reported the relationship between the short-term and long-term prognosis of acute heart failure (AHF) and acute kidney injury (AKI) based on the risk, injury, failure, and end stage (RIFLE) criteria. However, the relationship between the short-term and long-term prognosis and the timing of AKI during the first 7 days has not been reported.

Methods: Six hundred twenty-five patients with AHF admitted to the intensive care unit were analyzed. The occurrence of AKI was evaluated by the RIFLE classifications during the first 7 days after admission. AKI presented upon admission or occurred after admission in 174 patients (late-AKI), however no AKI occurred in 281 patients (no-AKI). Patients assigned into three categories by the severest degree of AKI during 7 days after admission: Class R (risk; n=214), Class I (injury; n=73), or Class F (failure; n=57). The study evaluated the relationships between the presence of AKI (its timing and degree) and outcomes, including short term prognosis (in-hospital mortality) and long term prognosis (any-cause death and HF events, including death and readmission for HF within 2 years).

Results: A multivariate logistic regression model found the presence of AKI during first 7 days to be independently associated with in-hospital mortality (p=0.002; OR: 3.633; 95%CI: 1.591-8.297). Kaplan-Meier survival curves showed that the prognosis, including any-cause death, was significantly poorer in early-AKI than in late-AKI and no-AKI, and was significantly poorer in late-AKI than in no-AKI. A multivariate logistic regression model found that Class I (p=0.003; OR: 4.040; 95%CI: 1.610-10.137) and Class F (p=0.001, OR: 6.427; 95%CI: 2.616-15.914) were independently associated with in-hospital mortality. The Kaplan-Meier survival curves showed the prognosis, including any-cause death, to be significantly poorer in Class I than in no-AKI and Class R, to be significantly poorer in Class F than in no-AKI, Class R and Class I, the prognosis including HF events to be significantly poorer in Class F than in no-AKI, Class R and Class I.

Conclusions: The presence of AKI during the first 7 days was independently associated with short-term prognosis; furthermore, the presence of AKI on admission was associated with long-term mortality for AHF. The presence of severe AKI (Class I and F) during the first 7 days after admission was associated with both short-term and long-term prognosis for AHF. The RIFLE criteria should, therefore, be developed into a clinically applicable and standardized method for AHF patients.

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Prevalence and predictors of sleep-disordered breathing in patients with chronic stable heart failure: the SchlaHF-Registry

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Objective: In patients with stable chronic heart failure (CHF) we investigated the prevalence and predictors of sleep-disordered breathing (SDB).

Patients and Methods: The ongoing multi-center SchlaHF registry provides demographics and clinical data on stable CHF patients. We included prospectively 3504 CHF patients from cardiology practices and cardiology departments of hospitals in our analysis. Inclusion criteria are New York Heart Association (NYHA) class III and IV, and left-ventricular ejection fraction (LVEF) ≤45%. SDB, defined as apnea-hypopnea index (AHI) ≥15/h, was determined by a two-channel screening (nasal airflow, pulse oximetry) using ApneaLink (ResMed, Sydney, Australia).

Results: The prevalence of SDB was 36% in women (n=739), 48% in men (n=2765) and 46% in the entire sample of CHF patients. Prevalence of SDB rose with increasing age (≥50, 50-60, ≥60-70, >70-80 and >80 years) from 30% to 40%, 45%, 52% and 56%, respectively. Risk factors for SDB were male gender (odds ratio [OR] 1.77; 95% confidence interval [CI] 1.49-2.11), age (OR 1.36, 95% CI 1.28-1.45 per 10-year age increment), obesity (body mass index ≥30kg/m2; OR 1.53, 95% CI 1.31-1.77), severe impairment of cardiac function (LVEF <25%; OR 1.24, 95% CI 1.07-1.43), highly symptomatic CHF (NYHA class III and IV vs. NYHA class II; OR 1.19, 95% CI 1.03-1.38), and atrial fibrillation (OR 1.28, 95% CI 1.08-1.51).

Conclusions: The multi-center SchlaHF registry shows that prevalence of SDB is high in a representative sample of stable CHF outpatients. Male gender, obesity and severity of CHF are clinical predictors for SDB.

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Incidence of impaired pulmonary function in men with systolic heart failure and its clinical significance

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Background: Impaired pulmonary function is often seen in systolic heart failure (HF), however, there is little data about its incidence and clinical determinants.

Methods: Spirometry and cardipulmonary exercise test (CPX) were performed in 204 men with stable systolic HF (age: 57±11 years, LVEF: 30±8%, ischaemic aetiology: 49%, NYHA class III/IV: 56/113/31), none of them had previously diagnosed lung disease and related therapy. Almost all men were taking b-blockers (99%) and ACE inhibitors or ARB (100%), Forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were assessed according to American Thoracic Society/European Respiratory Society Guidelines, and expressed in litre (L) and % of predicted values.

Results: Normal spirometry results (FEV1/FVC ≥70%, FVC ≥80%) pred.) was found in 112 (55%) men with HF, only obstructive pattern of breathing (FEV1/FVC <70%, FVC >80% pred.) in 16 (8%) men with HF, only restrictive pattern of breathing (FEV1/FVC ≥70%, FVC <80% pred.) in 49 (24) men with HF. The combination of these two abnormalities (FEV1/FVC <70%, FVC <80% pred.) in 27 (13%) men with HF. Clinical characteristics of these groups are presented in table.

Conclusions: Impaired pulmonary function is common in men with systolic HF.
Are functional and absolute iron deficiencies equally detrimental in heart failure?

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Introduction: Iron deficiency (ID) has shown to worsen prognosis in patients with heart failure (HF). ID can be absolute or functional.

Objective: To assess the prognostic significance of ID (both absolute [defined as ferritin <30 μg/L] and functional [defined as ferritin ≥30 μg/L and transferrin saturation <20%]) in a real-life HF outpatient population.

Patients: 678 patients (72% men, median age 70.3 years [IQR 60.5-77.2]) were studied. Aetiology of HF was mainly ischemic heart disease (52.2%). Median LVEF was 34% [IQR 26-43%]. Most patients were in NYHA class II (65.6%) or III (26.3%). Median follow-up was 3.4 years [IQR 1.84-5.04].

Results: ID was present in 452 patients (51.1%), being absolute in 81 (9.2%) and functional in 371 (42.3%). Only 238 patients with ID were anaemic (52.7%). During follow-up 313 deaths were recorded. ID was associated with higher mortality (HR 1.66 [IQR 1.18-2.34, p=0.004]. In the multivariable analysis (backward step), ID only remained an independent predictor in non-anemic patients.

Conclusion: IRON deficiency is an independent predictor of mortality in patients with heart failure.
Surgery for valvar heart disease: predictors of outcome

Methods: 850 patients (mean age, 57.9±8.3 years) from 2000 to 2010, with coronary artery diseases and significant ischemic mitral regurgitation (≥2) were operated – in 787pts CABG + MV repair were performed and in 63 pts MV replacement were combined with CABG. Groups were matched by propensity score using demographies dates, co-morbidity, coronary status, LV remodeling, MV deformation and MR grade by quantitative echocardiography. Survival (with mean follow-up 4.8±3.5 years) and New York Heart Association functional class were compared. The impact of mitral valve replacement versus repair on survival by comparing these propensity matched subgroups was analyzed.

Results: Follow-up was 100% complete. Before matching 10-year survival was significantly worse in replacement group (long-rank p=0.003). After propensity matching we’ve received homogenous cohort of 69 pts with severe compro-

similarities propensity matched subgroups was analyzed.

Conclusions: The mitral valve replacement versus repair did not influence survival (long-rank p=0.443) and overall in 1- and 5-year survival it was 91.8±0.1/4% and 69.2±0.48%, respectively. The independent risk fac-
tors for an increased mortality within the five years of surgery in multivariate propensity-matched analyses were found LV ESD (HR=1,085, 95% CI 1.018–1.157, p=0.013), cross-clamp time (HR=1.028, 95% CI 1.006–1.05, p=0.012), use of IABP during hospital period (HR=3.147, 95% CI 1.7–8,4, p=0.001) and age (HR=0.936, 95% CI 0.876–1.0, p=0.011).

Different surgical techniques of mitral valve repair for ischemic mitral regurgitation: predictors of efficacy


Objective: Mitral valve annuloplasty is the standard surgical option for the management of ischemic mitral regurgitation (MR). However, after annuloplasty recurrent MR develops in some patients.

Methods of the Investigation: Preoperative echocardiographic dates from consistent 787 patients who underwent MV repair for ischemic MR combined with revasculation were prospectively collected and reviewed. Of the 787 patients, 53 (8,1%) had residual MR ≥2 grade during even during hospital stay. The mitral valve and LV parameters, including tethering area and coaptation height of the mitral leaflets, were determined. SPSS 15.0 statistics was used.

Results: The type of annuloplasty (rigid ring, flexible ring or posterior annul-

plasty) hadn’t influenced the efficacy of surgical treatment (occurrence of the residual MR ≥2 grade was 7%, 5,6% and 4,5% corresponding, x²=1,75, p=0.416). On ROC-analysis and multiple logistic stepwise regression analysis from 277 patients, a large LV (EDD ≥ 65 mm, OR 2.7, 95% CI 1.12-6,56, p=0.027; EF < 59.5 mm, OR 2.5, 95% CI 1.36-6,50, p=0.042, EDV > 105 mm³, OR 3.41, 95% CI 1.42-8.29, p=0.007 and IESV ≥ 66 mm², OR 2.63, 95% CI 1.12-6,24, p=0.03) were identified as independent predictors for failure of MV repair without rigid ring (flexible or semirigid ring, commercially available or xenopericardial posterior band and else). From 378 cases the higher tethering area (for apic4ch viewer area (for apic4ch viewer ≥ 2.5 mm² OR 5.06, 95% CI 1.1-34.7, p=0.04 and for apic ≥ 1.5 mm² OR 8.01, 95% CI 1.46-43.7, p=0.016) and higher MR severity (for vena contracta ≥ 6.5 mm OR 1.56, 95% CI 1.02-2.3, p=0.02 and for ERO PISA ≥ 0.39 mm² OR 1.07, 95% CI 1.02-1.15, p=0.05) were identified as independent predictors for failure of MV repair.

Conclusion: In conclusion, these results demonstrated that preoperative findings of precise echocardiography can be used to identify patients with ischemic MR at increased risk of repair failure.

Comparison of risk scores for predicting early mortality after Aortic Valve Replacement for aortic stenosis


Background: Major risk scores of early mortality in cardiac surgery are the Soci-

ty of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score and the European System for Cardiac Operative Risk Evaluation (EuroSCORE) score. A new model of EuroSCORE, which is called EuroSCORE II, was launched at 2011.

The aim of this study was to compare STS-PROM and EuroSCORE II after AVR for AS.

Methods: We analyzed the data from 258 consecutive patients who underwent AVR at Juntendo University and or CABG, between 2002 onwards. Observed versus expected (O/E) mortality rates were examined. Hosmer-Lemeshow goodness-of-fit test and receiver operating characteristics (ROC) curves were performed to assess the performance of these models.

Results: Observed early mortality was 4.2% (n=11). Predicted mortality rates for STS-PROM and EuroSCORE II was 4.7% and 3.5%, respectively, and thus the O/E ratios for STS-PROM and EuroSCORE II was 0.89 and 1.20, respectively. Pearson correlation coefficient revealed a good linear relationship between STS-

PROM and EuroSCORE II (r = 0.76, p < 0.001). Hosmer-Lemeshow goodness-of-fit test indicated good accuracy for the prediction of mortality for both models (r = 0.801 for STS-PROM and 0.588 for EuroSCORE II). The area under the ROC curve was 0.79 (95% CI: 0.63 to 0.96) for STS-PROM and 0.69 (95% CI: 0.49 to 0.89) for EuroSCORE II, implying that the discrimination ability of STS-PROM was better than that of EuroSCORE II.

Conclusions: There was a slight trend toward overestimation in STS-PROM (O/E ratio; 0.89) and underestimation in EuroSCORE II (O/E ratio; 1.20). STS-PROM is better than EuroSCORE II in terms of discrimination ability. These results have implications for risk judgment in AVR for AS.

46.1 ± 13% vs 62 ±13%, 46.1 ± 15% vs 57 ±10% and 37.5 ± 10 mm Hg vs 31 ±10 mm Hg (p < 0.001, 0.039 and 0.033), respectively.

Conclusion: Perioperative mortality risk and death rate seems to be related to AS severity in patients undergoing isolated AV replacement.

Predictors of persistent severe diastolic dysfunction after aortic valve replacement in aortic stenosis compared with aortic regurgitation

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Purpose: 1. To evaluate the effect of aortic valve replacement (AVR) on left ventricular (LV) diastolic function and LV remodeling, comparing patients with aortic stenosis (AS) to patients with aortic regurgitation (AR).

2. To identify the parameters appropriate for prediction of immediate and medium term evolution in these patients.

3. To assess the independent predictors for persistence of the restrictive LV diastolic filling pattern (LVDVF) after isolated AVR.

Methods: Five years prospective study on 397 patients with restrictive LVDVF un-
dergoing AV for AS (Group A - 226 pts) or AR (Group B - 171 pts). Patients were evaluated preoperatively and at 10 days, 1, 3, 6-months, 1 year and yearly 5 years postoperatively. Depending on the LVEF, each of the two groups was divided into 2 subgroups: pts with LVEF<50% (Group A1-137 pts and group B1-102pts) and pts with LVEF>50% (group A2-99 pts and group B2-68 pts). Statistical analysis used STATXAS and SPSS programs for the simple and multiple regression analysis and relative risk calculations.

Results: 1. The evolution of the LV diastolic function was different in AS group (after AVR diastolic filling improved) compared with AR group. At 1 year post-surgery the percent of the patients with persistent restrictive LVDVF was 23.01% in AS group and 60.23% in AR group.

2. At 5 years, cardiovascular event-free survival, including hospital visits caused by heart failure symptoms and sudden cardiac death was significantly higher in the patients with preoperative AS (87,17%) compared with AR group (64,91%).

3. The parameters appropriate for prediction of immediate and medium term evolution were: preoperative NYHA class, LVEF, atrial fibrillation, coronary artery disease and smoking.

4. Simple and multivariate regression analysis identified as independent pre-

dictors for persistence of a restrictive LVDVF: AR (RR=19.2), E/E ratio; 0.89) and underestimation in EuroSCORE II (O/E ratio; 1.20). STS-PROM is better than EuroSCORE II in terms of discrimination ability. These results have implications for risk judgment in AVR for AS.
Conclusions: 1. Restrictive flow pattern is reversible mostly after AVR for AS than for AR, both in the early and medium postoperative term. 2. The parameters predicting fatal outcome and hospitalisation for heart failure on mortality above 75% in the early postoperative NYHA class, LVEF, atrial fibrillation, coronary artery disease and smoking. 3. The echocardiographic predictors for persistence of a restrictive LVFP in patients with AR and LV systolic dysfunction were the LA dimension index >30mm²/m², severe PHT and associated 2 degree MR.

Need for permanent pacemaker implantation after corevalve, sapien and surgical aortic valve replacement: incidence, time course and predictive factors

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Purpose: To compare the incidence of complete atrioventricular block (AVB) and permanent pacemaker implantation (PPM) following transcatheter aortic valve implantation (TAVI) versus standard aortic valve replacement (SAVR), and to determine the factors associated with PPM following TAVI or SAVR.

Methods: We analysed data from 340 patients (pts) with severe aortic stenosis (SAS) and no prior pacemaker who underwent TAVI with either the CoreValve (n=132) or Edwards-Sapien (n=208) prosthesis between 2007 and 2011 and from 210 patients (pts) undergoing SAVR between 2005 and 2009 at one centre. The incidence, reasons, and predictive factors for PPM following the procedure were compared between groups.

Results: The incidence was similar in both groups (TAVI: 7.6±7.3 years; SAVR: 9.07±7.8 years, p>0.05), and the TAVI group exhibited a higher risk profile (Log EuroScore 22.9±15.8% vs. 13.1±11.6% in the SAVR group, p<0.001). The rate of new PPM was higher following TAVI (n=50, 15.7%) compared to SAVR (n=2, 0.97%), p<0.001. The main causes of PPM implantation were: third degree atrioventricular block (TAVI: 39pts, 78%; SAVR: 2pts, 100%), atrial fibrillation with a ventricular rate lower than 40/min (TAVI: 3pts, 6%), second degree atrioventricular block (TAVI: 3pts, 6%), and progressive QRS widening (TAVI: 3pts, 6%), and bradycardia-tachycardia syndrome (TAVI: 1pt, 2%). The median time from TAVI to implantation of a PPM was 2 days (interquartile range 1-7 vs. 14 days (interquartile range 12-15). Complete-AVB was the primary reason for PPM in the TAVI (78%) and SAVR (100%) groups (p<0.001). In the TAVI group, complete AVB was more common after implantation of a Corevalve than Edwards prosthesis (64.1% vs. 35.9%, p<0.001). On multivariable analysis, the predictors of PPM for advanced AVB, atrial fibrillation, left ventricular dysfunction, LA diameter, AF cycle length, and duration of continuous AF were predictors of PPM following TAVI in the TAVI group. In the SAVR group, LVEF below 35% (OR:2.1, 95%-CI:0.9-4.9, p<0.05) was associated with a significant risk of PPM.

Conclusions: In pts with persistent AF, stepwise ablation with repeat intervention procedure provides good long-term outcome even with strict definition for failure (AF ≥30sec). A slow decline of arrhythmia-free survival is noted over 5 years FU. Procedural termination of AF predicts long-term arrhythmia-free survival.

Additional ablation of complex fractionated atrial electrograms in long-lasting persistent atrial fibrillation: Does it change the ablation success? Results from the German ablation registry

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Introduction: In therapy of paroxysmal and long-lasting persistent atrial fibrillation (AF) pulmonary vein isolation (PVI) is a well-established therapeutic option. In ablation of long lasting persistent AF substrate modification is usually required. Additional ablation of complex fractionated atrial electrograms (CFAE) has been used as an additional option in ablation.

Hypothesis: Does ablation of CFAE in addition to PVI lead to a change of ablation success in patients with long-lasting persistent AF?

Methods: In 55 patients the patient and procedural data as well as acute and long-term outcome data from 435 pts. (mean age 63.3 yrs., 340 m, 95 f) with ablation of long-lasting persistent AF were prospectively collected. One-year follow-up (1yFU) was performed by telephone call. Data collection and the statistical analysis were performed for the German Ablation Registry organized by an Institut, Ludwigsafen, Germany.

Results: In 160 consecutive pts with persistent AF undergoing de novo catheter ablation of long-lasting persistent AF was performed without and in 110 Pts. with additional ablation of CFAE. The baseline clinical characteristics were not different except more re-do procedures in the CFAE group (38,3% vs. 21,8% p<0.01) and more pts. with left ventricular dysfunction in the non-CFAE group (24,0% vs. 8,8% p<0.001). The acute success rate (96,6% without vs. 91,8% with CFAE p<0.05) and the acute recurrence rate of AF until hospital discharge (12% without vs. 20,9% with CFAE p<0.05) were statistically significant different. The 1yFU data could be obtained in 73,6% of Pts. without CFAE ablation and in 69,8% of pts. with CFAE ablation. At 1yFU the recurrence rate was 57,4% without CFAE ablation vs. 53,2% with CFAE ablation (p=0,52). Median procedure time (200 vs. 175 min. p<0,01), duration of procedural acidosis (63 vs. 59,8 min. p<0,001) and the fluoroscopy time (33 min vs. 23 min. p<0,001) were longer in the CFAE pts. The dose area product (4052 cGy*cm² vs. 3835 cGy*cm², p=0,44) was not different in the groups.

Conclusion: These data suggest that ablation of CFAE in addition to PVI vs. PVI alone does not lead to a significant change in ablation success regarding the 1yFU recurrence rate of AF. The main limitations are: non-randomized registry data, incomplete follow-up, post-hoc analysis and especially the different contingent of re-dos in the groups.

Rhythm control in elderly patients with persistent atrial fibrillation: a randomized comparison of catheter ablation versus antiarrhythmic drugs

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Purpose: We conducted a prospective randomized study to compare efficacy and safety of catheter ablation versus antiarrhythmic drugs (AAD), in a cohort of elderly patients with persistent atrial fibrillation (AF).

Methods: 354 consecutive patients, aged > 70 years, were randomly assigned in a 1:2 fashion to catheter ablation (Group A: 118 patients) or AADs (Group B: 236 patients). Study endpoints were: treatment failure, defined as any atrial arrhythmias lasting > 3 minutes, and treatment-related adverse events (acute when ≤ 1 month of procedure and long-term when > 1 month of procedure).

Results: At a mean follow-up of 42±17 months, 45% of Group B patients were in sinus rhythm (SR) vs. 53% of Group A and 75% of continuous AF at 1 month blanking period. A minimum follow up (FU) of 48 months with repeated Holter monitoring was performed. Arrhythmia recurrence was defined as AF or AT ≥30 sec. Interim analysis of the first 75 pts (51.55±9 years, LVEF 57±14%, 50% long-standing PaF) had completed FU is presented.

Results: AF was terminated during the index procedure in 60 of 75 pts (80%). LA size, QRS cycle length, and duration of continuous AF were predictors of AF termination (All p<0.05). Arrhythmia-free survival rates were 46%, 31%, and 20% after a single procedure, and were 84%, 79%, and 67% after multiple procedures (2.2±1.1 procedures; median=2 (1-3) at 1, 2, and 5 years FU, respectively. At 5.3±1.9 years, 75 pts (78%) were free of any recurrences (n=55; 67%) or showed clinical improvement (> 90% AF burden reduction) under previously ineffective antiarrhythmic drugs (n=17; 7%). Most recurrences occurred over the first 6 months. Duration of continuous AF (13±13 months vs. 23±25 months; p<0.05) and termination of AF during index procedure (75% vs. 29%; p<0.01) were associated with freedom from arrhythmia recurrence. In multivariate analysis, only termination of AF was an independent predictor of freedom from AF (OR 1.195, 95% IC 1.057-1.350) and AF duration at the procedure (OR 1.011, 95% IC 1.001-1.021). Fifteen acute adverse events occurred (12 in Group A vs. 3 in Group B, p<0.001), mainly periprocedural cerebral thromboembolism (6 in Group A vs. 2 in Group B, p<0.02). The independent predictors of post-ablation cerebrovascular accidents were previous transient TIA/stroke (OR 1.195, 95% IC 1.057-1.350) and AF duration at the procedure (OR 1.011, 95% IC 1.001-1.021). At follow-up, 69 long-term adverse events occurred (12 in Group A vs. 57 in Group B, p<0.001). Group B patients resulted associated with a significant...
Incidence and management of potentially fatal peri-procedural tamponade in patients undergoing pulmonary vein isolation for atrial fibrillation

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Purpose: Pulmonary vein isolation (PVI) has emerged as an effective treatment option for atrial fibrillation. However, it may be complicated by potentially life-threatening complications such as cardiac tamponade. We sought to assess incidence, circumstances, management and outcome of peri-procedural cardiac tamponade over the last 5 years in 2 high-volume interventional electrophysiology centres.

Methods: Since January 2007, a total of 4558 PVI procedures were performed in 3233 patients with AF (65±11yo, 71% male, 39% persistent AF). Patients underwent (3D)Lasso-guided wide circumferential PVI. Transseptal puncture was guided by TEE in 1950 procedures. Patient characteristics, comorbidities and procedure-related details of major adverse events were recorded immediately after procedure in a central database. We analyzed all tamponades with hemodynamic compromise necessitating intervention with regard to timing, underlying mechanism, management and outcome.

Results: Peri-procedural cardiac tamponade occurred in 27 patients (0.59% procedures). Tamponade occurred acutely (during procedure) in 25/27 patients and in 2/27 patients as an inflammatory reaction within the 2 weeks following the PVI. Urgent surgery was necessary in 6/27 cases (0.17% of all procedures; 29.6% of tamponades). In 2/8 cases pericardioceintesis failed; in the remaining 6/8 cases immediate operation was necessary because of continuous bleeding, despite antitagonism of anticoagulation and successful pericardiocentesis. In all 8 cases surgical intervention was urgently necessary to overcome fatal outcome; in 3 cases the surgical intervention was performed in the catheter lab. The source of hemorrhage in 5/8 cases was perforation of the left atrial appendage and in 3/8 pop and perforation of anterior/intercaval LA wall and remained undetermined in 1 case. The outcome was favourable in all 27 patients, hospital stay was delayed by 3±4 days.

Conclusions: Cardiac tamponade necessitating intervention occurs in 0.59% of PVI procedures. 29.6% of peri-procedural cardiac tamponades necessitate urgent cardiac surgery, in order to prevent fatal outcome. Late tamponade after hospitalisation due to an inflammatory reaction occurred in 2 patients (0.04% of procedures, 7.4% of tamponades).
mortal regurgitation grading significantly decreased (p<0.001) only within these patients. At multivariable analysis SR maintenance emerged as an independent predictor of long-term clinical improvement (Odds Ratio 4.26 95%CI 1.69-10.74, p<0.002).

Conclusions: Although not substantially worse than in patients with preserved LV EF, AF ablation in patients with impaired LV EF is affected by high long-term recurrence rate. Amongst these patients SR maintenance is associated with greater clinical improvement.

TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI)
IN CURRENT AND FUTURE CLINICAL PRACTICE

3874 Early experience with the JenaValve transapical aortic valve implantation system

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Transcatheter aortic valve implantation (TAVI) has become a well accepted clinical option for treating high risk patients suffering from severe symptomatic aortic valve stenosis. The self-expanding JenaValve prosthesis consists of a nitinol stent with a porcine root valve available in three different sizes. The stent is fixed in orthotopic position by clipping on the cusps of the old diseased valve. The three-step implantation procedure can be performed under beating heart conditions avoiding hemodynamic compromise. The retrievable and repositionable system received CE-mark in September 2011. Three months results of all pre CE-mark implantations are summarized in this report.

3875 The impact of pulmonary hypertension on outcome in TAVI patients: a two-centre experience

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Background: The prognosis of patients with aortic stenosis (AS) and pulmonary hypertension (PH) is poor though not fully understood. Transcatheter aortic valve implantation (TAVI) facilitates treatment of patients in end-stage AS many of whom are suffering from severe PH. The aim of our study was to elucidate the impact of PH on outcome after TAVI.

Methods and results: Pre and 90 days post TAVI, pulmonary artery systolic pressure (PASP) was determined non-invasively by echocardiography in 326 patients undergoing TAVI. PASP was classified as absent (<30mmHg), mild-to-moderate (30-60mmHg), and severe (>60mmHg). 327 patients (logistic EuroSCORE: 26.9±8.8mmHg to 50.2±12.3mmHg, P<0.001). In 22 (26%) pts had coronary artery disease (CAD), 66 (77%) had mitral annulus calcification (MAC) and 38 (44%) had organic mitral valve disease (OMVD). No relation was found between presence of CAD, MAC or OMVD and improvement of MR degree or VC (P>0.2 for all). In 22 (26%) pts MR improved by 1 grade, 5 (6%) by 2 grades, 1 (1%) by 3 grades, no change in 66 (77%) had mitral annulus calcification (MAC) and 38 (44%) had organic mitral valve disease (OMVD). No relation was found between presence of CAD, MAC or OMVD and improvement of MR degree or VC (P>0.2 for all). In 22 (26%) pts MR improved by 1 grade, 5 (6%) by 2 grades, 1 (1%) by 3 grades, no change in 45 (52%) and worsening in 13 (15%) pts.

3876 Is mitral regurgitation reversible in patients undergoing transcatheter aortic valve implantation?

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Background: Significant mitral regurgitation (MR) is often present in pts with severe aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI). Detection of MR in such pts is crucial as it can independently affect functional status and prognosis.

Methods: Comprehensive echocardiographic studies were performed in all TAVI pts before procedure and before hospital discharge. MR was classified according to vena contracta (VC) and visual assessment as absent, mild, moderate or severe.

Results: In our department, 86 pts underwent successful TAVI since 2008. A balloon expandable valve was implanted (Edwards-Sapien- 79 pts, Medtronic-7 pts); 70 by retrograde transfemoral, 14 by anterograde transapical and 2 by subclavian approach. Aortic peak/mean gradient in pre and post TAVI were 85.1±26.8±31.6±16mmHg and 23.4±10.12±9.9±7mmHg respectively (p<0.001 for both). Mild aortic incompetence (AI) post TAVI was observed in 27 (31%) pts, moderate in 18 (21%) pts. No patient had severe AI. Severity of MR: visual assessment (see Table). Mean VC was 0.41±0.17cm before TAVI and 0.38±0.16 after procedure (p<0.001). First order of the self-expanding transapical JenaValve TAVI system showed promising result with respect to a low rate of aortic regurgitation at follow-up. Ongoing studies will further evaluate this TAVI device in high risk aortic stenosis patients.

3877 Perivalvular aortic regurgitation: a major predictor of 1-year mortality after a successful TAVI procedure - Insights from the FRANCE2 registry

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Background: A significant peri-valvular aortic regurgitation (AR) is observed in 15-20% of the cases after a successful transcatheter aortic valve implantation
The impact of transcatheter aortic valve implantation on resource use. Results from the German transcatheter aortic valve interventions registry

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Purpose: Transcatheter aortic valve implantation (TAVI) has been shown to improve survival compared with standard therapy in patients with severe aortic stenosis who are ineligible for surgery. Especially older patients with aortic stenosis cannot always be offered conventional surgical aortic valve replacement at an acceptable risk. Therefore TAVI is currently an alternative treatment option. The effects of TAVI on resource use regarding hospital stays have not been reported from a large scale cohort.

Methods: Patients with symptomatic, severe aortic stenosis are included in the prospective multicentre German transcatheter aortic valve interventions registry since 2009. This registry monitors current use, outcome of transcatheter aortic valve interventions in daily clinical practice, and assesses safety, effectiveness and health economic data. We performed an analysis regarding inpatient hospital stays for a subset of patients who underwent TAVI and completed the one-year follow-up. These results refer to hospital stays one year before and after TAVI.

Results: Resource use data were eligible for 415 patients who survived 12 months after TAVI (average age 81.9±9.5 years; men 73.7%). In the year before TAVI, 2.4% had an inpatient hospital stay. Among this the average number due to cardiovascular causes was 2.0±1.2, indicating the clinical relevance and severity of this heart disease. Of those patients who give information about hospital stays (n=354) 33.6% had one admission (2 admissions: 29.4%; 3 admissions: 4.9%; ≥ 4 admissions: 5.4%) due to any cause. 12 months after the TAVI procedure 35.2% (142/403) of the patients had at least one hospital stay. The median duration till rehospitalisation was 25.7±17.5 weeks. The Kaplan-Meier estimation for the one-year rehospitalisation rate was 30.2%. Patients with rehospitalisation had on average 1.5±0.9 admissions with a median duration of 2.5±2.9 weeks. Of those patients who give information about the number of hospital stays 70.4% reported one admission due to any cause (2: 20.0%, 3: 5.9%, ≥4: 3.7%, ≥5: 3.0%).

Conclusions: Among patients from the German transcatheter aortic valve interventions registry with severe aortic stenosis TAVI resulted in meaningful reductions in resource use regarding inpatient hospital stays one year after TAVI.

The authors are grateful to the members of all clinics, which provided data to the German transcatheter aortic valve interventions registry.

NEW INSIGHTS IN MYOCARDIAL INFARCTION BY MULTIMODALITY IMAGING

Effect of manual thrombus aspiration during primary percutaneous coronary intervention on infarct size: a delayed enhancement MDCT study

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Objectives: We sought to assess whether manual thrombus aspiration could reduce infarct size in patients with acute STElevation myocardial infarction (MI) undergoing primary percutaneous coronary intervention (PCI).

Background: The efficacy of manual thrombus aspiration during primary PCI for acute MI remains controversial.

Methods: Between April 2009 and Mar 2011, 86 consecutive patients presenting with first acute STEMI (Killip=II) within 12 hours after the symptom onset underwent randomized thrombus aspiration (group I, N=44) or conventional PCI without thrombus aspiration (group II, N=42). The use of glycoprotein IIb/IIIa inhibitor (GPI) was left to the discretion of the operator. All patients received aspirin 300 mg and clopidogrel 600 mg before PCI and underwent delayed enhancement (DE) multi-detector computed tomography (MDCT) immediately after PCI without injection of an additional contrast media for assessment of infarct size, determined as the total volume of myocardium showing DE. DE MDCT was repeated at 2 months after PCI. The primary endpoint was infarct size reduction at 2 months. Baseline clinical characteristics and angiographic findings were similar between the 2 groups. There were no differences between group I and II in symptom-to-door-time (204±205 min vs. 217±168 min), door-to-balloon-time (70±42 min vs. 69±25 min), PCI-to-MDCT time (17±15 min vs. 13±6 min), Pre-PCI TIMI 0/1, Pre-PCI TIMI 2, or the use of GPI. Markers of myocardial necrosis showed similar trend before PCI but had no significant difference: ST-resolution rate >70% (74% vs. 65%), myocardial blush grade 3 (88% vs. 68%), and corrected TIMI frame count ~28 (31% vs. 24%). Initial infarct size determined by DE MDCT and left ventricular ejection fraction (LVEF)
In vivo non invasive quantitative assessment of passive diastolic stiffness of infarcted myocardium using shear wave imaging

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Background: Quantitative imaging of myocardial stiffness is important for the evaluation of systolic (active) and diastolic (passive) LV function. No tool is available to quantify non-invasively myocardial stiffness, which is determinant in case of diastolic heart failure. Shear Wave Imaging (SWI) is a new non invasive ultrasound technique that was recently shown to quantify the time-varying myocardial stiffness in vivo. In this study, we investigate the potential of this new technique to quantify the stiffness in patients with diastolic heart failure.

Methods: SWI was performed in vivo on five open-chest sheep. A linear conventional ultrasonic transducer (8 MHz) was positioned on the LV anterior wall. Shear waves were generated remotely in the myocardium using the acoustic radiation force induced by the ultrasonic probe. The shear wave propagation was imaged in real-time using an ultrafast scanner prototype (12 000 frames/s, Supersonic imagine, France). The local myocardial stiffness was derived from the shear wave speed which were performed every 50ms to measure the stiffness variation within one cardiac cycle. Myocardial stiffness was also assessed invasively in the same region using the pressure-segment length relationship obtained by sonomicrometers (Sonometrics, Canada). The ligation of one diagonal of the left anterior descending coronary artery was achieved to induce ischemia during 2 hours, and repertusion was performed during 30 minutes. Measurements were made at baseline, during ischemia and after repertusion.

Results: Diastolic stiffness of the ischemic myocardium was found to increase after 45 minutes of ischemia. The shear wave speed increased from 0.8±0.16 m/s to 1.5±0.4 m/s (p<0.01). After repertusion, diastolic stiffness increased even more strongly and diastolic shear wave speed reached 2.8±1.1 m/s (p<0.002). The slope of the end-diastolic pressure-segment relationship, which increased from 10.3±2.4 to 31.6±16.2 kPa, confirmed the stiffening. The peak diastolic strain rate decreased from 2.43±0.35 s-1 to 0.82±0.33 s-1 (p<0.05) demonstrating impaired relaxation of the ischemic segment. Finally, TTC staining performed on the explanted myocardium confirmed the presence of a large infarcted zone.

Conclusion: SWI was able to quantify non-invasively the increase of passive diastolic myocardial stiffness in vivo model of ischemic heart failure.

Myocardial fibrosis and fat may be substrates of critical ventricular arrhythmia. comparison of 320 slice CT images in subjects who had ventricular fibrillation with sustained ventricular tachycardia

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Purpose: If specific organized substrates of ventricular fibrillation (VF) are identified, they may provide important information for prevention of sudden cardiac death. 320 slice CT can acquire heart images in one heart beat and even if arrhythmia occurs during acquisition, clear heart images can be obtained. We compared 320 slice CT heart images in subjects who had VF with those who had sustained and non sustained ventricular tachycardia (VT).

Methods: A total of 94 subjects who had VF (18 subjects; age, 57±16 yrs), sustained VT (18 subjects; 60±20 yrs) or non sustained VT (58 subjects; 59±15 yrs) underwent 320 slice CT (Aquilion one). If there was a contrast defect in myocardium in early phase, late phase acquisition was added, and if abnormal late enhancement was observed in the corresponding site, we diagnosed myocardial fibrosis (MF). If the contrast defect continued in late phase with CT values < -9 HU, we diagnosed myocardial fatty change (MFC).

Results: There were no significant differences of several factors except ratio of complete right bundle branch block as represented in the table. On CT, there were no significant differences in percentage of coronary arteries with >50% stenosis among the 3 groups, but MF was significantly more common in VF group (67%, all MF was in left ventricle) than in non sustained VT group (28%, p<0.05). MFC was significantly more common in sustained VT group (56%, half of MFC was in right ventricle) than in VF group (22%, p<0.05) and in non sustained VT group (29%, p<0.05).

Conclusion: Left ventricular longitudinal function and neurohormonal activation after acute myocardial infarction. A two dimensional speckle tracking study

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Background: N-terminal pro-B type natriuretic peptide (NT-proBNP) is released in response to increased myocardial wall stress and is associated with adverse outcome in acute myocardial infarction. However, little is known about the relation between longitudinal deformation indices and NT-proBNP.

Methods and results: We consecutively included 611 patients with acute myocardial infarction admitted to a tertiary centre and performed echocardiography within 48 hours of admission. Global longitudinal myocardial function was assessed using 2-dimensional speckle tracking (DSTE) simultaneously with measurement of plasma NT-proBNP. A significant linear relation between NT-proBNP and global longitudinal strain (GLS) was found (p<0.0001, r=0.62). Weaker correlation was found between NT-proBNP and left ventricular ejection fraction (p<0.0001, r=0.44). GLS emerged on multivariable analysis including age, sex, estimated glomerular filtration rate, Killip class, diabetes, hypertension, presence of ST segment elevation, anterior infarction, Troponin level, Left atrial volume index, mitral valve deceleration time and E/e as the strongest predictor of logNT-proBNP (p<0.0001). In patients with preserved systolic function (LVEF >45%), GLS remained strongly correlated with NT-proBNP (p<0.0001). The C statistic associated with prediction of upper versus lower quartiles of NT-proBNP was significantly higher for GLS compared to LVEF (0.76 vs. 0.56; p<0.0001).

Conclusion: Two-dimensional longitudinal strain is more accurate than three-dimensional longitudinal strain to identify infarcted LV segments in STEMI patients


Purpose: To compare 2D vs 3D longitudinal strain (LS) in normal hearts and in patients with recent STEMI.
Methods: In 123 healthy subjects (aged 44±14 years, range 18-75) and 46 patients (58±13 years) with recent STEMI, three apical LV views for measuring 2D-LS (70±9 fps) and 4-beat LV full-volume data sets (31±4 fps) for measuring 3D-LS were acquired 8.2±1 days after primary PCI using Vibrant E9 scanner and analyzed with dedicated software (BT11, GE Healthcare, Horten, N). All subjects were selected for good image quality, sinus rhythm and adequate 2D/3D speckle tracking in at least 14 of all 17 segments. In pts, 2D-LS and 3D-LS were compared against 3D wall motion score (WMS) and delayed-enhancement at magnetic resonance (DE-MRI) performed ≥24h apart from echo study, both at segmental and global levels.

Results: In healthy subjects, global 2D-LS values were significantly lower than 3D-LS (-2.1±1.9% vs -19.1±2.1%, bias 1.3±2.2%, p≤0.001), with whom were also weakly correlated (r=0.37, p=0.001). In pts, global 2D-LS had closer correlations with infarct size index at DE-MRI, 3D WMS index and EF (r=0.65, 0.70, -0.68) than global 3D-LS (r=0.36, 0.48, -0.56, respectively, p<0.01 for all). Segmental 2D-LS values showed a higher discriminative power (F ANOVA = 144 vs 50 for 2D-LS vs 3D-LS, p≤0.0001) to separate normal segments from those with non-transmural and transmural necrosis (DE 0-50% and >50 for 2D-LS vs 3D-LS, p<0.0001) to identify segments with (dys)kinesia (AUC 0.81 vs 0.70) or transmural necrosis (AUC 0.83 vs 0.73, p=0.0001 for all).

Conclusions: Significant differences were identified between 2D-LS and 3D-LS in both normals and STEMI patients. Between the two tested vendor-specific algorithms, 2D-LS was more accurate than 3D-LS to identify infarcted LV segments and to reflect global LV dysfunction in STEMI patients.

Necrosis and ischemia for risk stratification in patients with known or suspected ischemic cardiomyopathy.

Methods: 274 patients with depressed ejection fraction (<50%, 38±9%) referred for study with stress CMR for known or suspected ischemic cardiomyopathy. We quantified (number of segments, s) the presence of severe ischemia (dipyridamole-induced perfusion deficit and wall motion abnormalities) and the extent of necrosis (late gadolinium enhancement in >50% wall thickness). We considered abnormal if more than one segment was altered.

Results: Ischemia and necrosis were ruled out in 89 patients (32%). Necrosis in 184 (67%) and severe ischemia in 22 (8%). During a median of follow-up of 329 days, 28 first events were detected (10%, death or infarction). Patients were excluded when suffered a major event or revascularization. More major events were detected in patients with necrosis (12% vs 7%, p=0.1) and especially in those with severe ischemia (45% vs 7%, p<0.001). After adjusting for baseline characteristics and CMR indexes, predictors of major events were (HR with 95% CI) end-systolic volume (1.01 [1.01-1.02] per m/m², p<0.001), extent of necrosis (1.1 [1.01-1.1] per s, p=0.02) and extent of severe ischemia (2.1 [1.7-2.7] per s, p<0.001).

Risk of major events was higher (p<0.001) in patients with severe ischemia (45%) compared with those with necrosis but without ischemia (8%) and those without necrosis or ischemia (6%).

Conclusions: In patients with known or suspected ischemic cardiomyopathy, the presence of severe ischemia is the most powerful prognostic index. A simultaneous study of viability and ischemia is recommendable for risk stratification.

METHODS OF OUTCOME IN CARDIAC ARTERY DISEASE

P3908
NSAID use is associated with an increase in adverse cardiac events: 4-year results from the REACH registry

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Background: There have been conflicting results regarding the risk of non-steroidal anti-inflammatory drugs (NSAIDs) in high-risk patients or those with established atherosclerotic disease. These medications have been linked to salt and water retention, adverse ventricular remodeling, and heart failure (HF). For this reason, we sought to assess their impact on cardiovascular (CV) events, HF, and hospitalizations for ischemic events.

Methods: We analyzed 63,747 patients in the REACH registry who had information available on baseline NSAID use and were followed for 4 years. Baseline characteristics were compared using Chi-square tests and Cox proportional hazard models were constructed and adjusted for all baseline characteristics with p<0.05. In addition, the interaction was assessed between NSAIDs and aspirin or platelet agents.

Results: Among patients receiving NSAIDs, the median age was higher (71 vs. 65) and there was a higher percentage of females, whites, and patients who weighed >60kg. More of those on NSAIDs had cardiac risk factors (hypertension, dyslipidemia, diabetes), baseline HF and creatinine clearance <60 mg/min (all p<0.001). There was a significant increased hazard associated with NSAID use for developing incident HF (HR 1.31, 95% CI 1.20-1.43, p<0.001), being hospitalized for ischemic events (HR 1.15, 95% CI 1.09-1.22, p<0.001), and in the composite endpoint of CV death/MI/Stroke/CV hospitalizations (HR 1.10, 95% CI 1.04-1.15, p=0.003) that persisted after fully adjusting for baseline differences in risk and for other clinical factors. There was no difference in CVDM/Stroke (HR 1.03, 95% CI 0.96-1.12, p=0.40). Following multivariable adjustment, NSAIDs were not associated with statistically significant increases in bleeding leading to hospitalization and requiring transfusion (HR 1.14, 95% CI 0.92-1.41, p=0.22). There was also no significant interaction between NSAIDs and aspirin (p-interaction=0.22) or NSAIDs and anti-platelet agents (p-interaction=0.21).

Conclusion: Among patients with stable atherothrombosis, NSAID use at baseline is associated with a higher risk of CHF, hospitalizations for ischemic events, and major adverse cardiac events.

P3909
History of stroke in patients with coronary artery disease in the REACH Registry: impact on cardiovascular and bleeding event rates

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Purpose: Several recent randomized trials have identified prior stroke as a marker of increased bleeding risk in coronary artery disease (CAD) patients receiving novel antithrombotics. We sought to evaluate the impact of history of stroke/TIA in CAD patients within a large international registry.

Methods and results: From the REACH registry of atherothrombosis, 26,389 patients with a history of CAD (of whom 4460 (16.9%) had prior stroke/TIA) and 4-year follow-up were analysed. Patients with prior stroke/TIA were older (70.5±9.7 years vs. 67.6±10.0 years, p<0.0001), more frequently female (34.1% vs. 29.2%, p<0.0001), and had higher baseline risks of bleeding and CV events. Patients with a history of stroke/TIA had increased risks of all-cause death, MI and stroke relative to patients without history of stroke/TIA. While total bleeding was not increased, non-fatal haemorrhagic stroke (HS) rates were increased in
these patients. In addition, among patients on dual antiplatelet therapy, there was a 7-fold (95% CI: 1.7-29.3) crude and a 4.9-fold (1.1-20.8) adjusted increase in the risk of non-fatal HS in patients with vs. without prior stroke/TIA. The excess risk of HS was greatest in the 1st year following a stroke/TIA (adjusted HR: 3.62, 95% CI: 1.67-7.85, p=0.0003), whereas beyond 1 year, risk was not increased (adjusted HR = 1.11, 95% CI: 0.47 – 2.61).

Crude and adjusted 4-year outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prior history of stroke/TIA</th>
<th>Crude HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>11.2 (2072) 17.8 (364) 1.67 (1.53 – 1.82)</td>
<td>0.0001 1.21 (1.10 – 1.32)</td>
<td>0.0001 0.98 (0.87 – 1.12)</td>
</tr>
<tr>
<td>MI</td>
<td>6.0 (1097) 6.8 (319) 1.46 (1.31 – 1.68)</td>
<td>-0.0001 1.22 (1.07 – 1.40)</td>
<td>-0.0001 0.98 (0.83 – 1.15)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.1 (739) 13.1 (448) 3.43 (3.06 – 3.85)</td>
<td>-0.0001 2.72 (2.41 – 3.08)</td>
<td>-0.0001 2.57 (2.19 – 3.04)</td>
</tr>
<tr>
<td>Total serious bleeds</td>
<td>2.5 (460) 3.5 (126) 1.39 (1.14 – 1.69)</td>
<td>0.001 1.06 (0.86 – 1.30)</td>
<td>0.001 1.06 (0.85 – 1.31)</td>
</tr>
<tr>
<td>Non-fatal haemorrhagic stroke</td>
<td>0.3 (49) 0.6 (19) 1.96 (1.16 – 3.34)</td>
<td>0.013 1.74 (0.99 – 3.03)</td>
<td>0.056 3.06 (1.54 – 6.13)</td>
</tr>
</tbody>
</table>

Adjustment included all baseline characteristics found to be independent correlates of prior stroke/TIA.

Conclusions: In CAD, a history of stroke/TIA is associated with an increased risk of death, MI, or stroke. However, it is also associated with a disproportionate increase in HS, particularly when patients receive dual antiplatelet therapy and in the first year following stroke/TIA. This suggests that while these patients are at high risk of cardiovascular events, increasing antithrombotic therapy carries a specific risk of HS.

P3910 Triple anticoagulant therapy following an acute coronary syndrome: prevalence, bleeding rate and utility of the HAS-BLED score

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Purpose: The aim of this study was to evaluate the prevalence of triple anticoagulant therapy (TT; warfarin, aspirin and clopidogrel) and associated bleeding risk, compared to double anticoagulant therapy (DAPT; aspirin and clopidogrel) in patients discharged from a Coronal Care Unit (CCU) following an acute coronary syndrome. Furthermore, we investigated the accuracy of the HAS-BLED risk score in predicting bleeding events in TT patients.

Methods: We retrospectively identified all patients from the Lund municipality on TT upon discharge from the CCU at Skane University Hospital in Lund between 2005 and 2010. TT patients were compared with age- and sex-matched controls discharged with DAPT. Major bleeding was defined in accordance with the HAS-BLED derivation study: Any bleeding requiring hospital care or causing a decrease in haemoglobin level of more than 20 mg/L or requiring blood transfusion.

Results: A total of 2423 patients were screened, of whom 159 (6.6%) were on TT. The mean age was 67.2 (±6.9) years. The most common indication for TT was atrial fibrillation (n=63, 46.9%) followed by apical aikinesia (n=60, 37.8%), and the mean duration of TT was 3.7 (±3.0) months. Upon termination of TT, Warfarin was discontinued in 82 (52.2%) patients and clopidogrel in 57 (36.3%). The cumulative incidence of spontaneous bleeding events was significantly higher in the TT group at one year (10.2% vs 3.2%, p<0.01). The HAS-BLED score significantly predicted spontaneous bleeding events in TT patients (area under the ROC curve 0.67, 95% CI = 0.54 – 0.79, p=0.048).

Conclusions: TT was relatively common following an acute coronary syndrome and associated with a threefold increase in major bleeding at one year compared to DAPT. The HAS-BLED risk score predicted bleeding events with moderate accuracy. Careful patient selection and clinical follow-up for TT appears warranted.

P3912 Prognosis of unrecognized myocardial infarction in elderly men and women: the Rotterdam Study

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Background: Unrecognized myocardial infarction (MI) is frequent in the general elderly population. Its prognosis is reportedly at least as unfavorable as that of recognized MI, particularly in men. However, contemporary data with long follow-up are lacking.

Objective: To investigate the long-term prognosis of unrecognized MI with respect to all-cause and cause-specific mortality, and to investigate any sex-differences in prognosis.

Methods: In the population-based Rotterdam Study (2072 men and 3862 women), we determined the presence of unrecognized MI and recognized MI at the baseline (1990-1993). The cohort was followed for nearly two decades for all-cause and cause-specific mortality.

Results: During 82,268 person-years of follow-up (median 15.6 years) 3,412 persons died (1300 due to a cardiovascular cause). Both men and women with unrecognized MI had an increased risk of all-cause mortality (Hazard ratio [95% confidence interval] = 1.72 [1.43 – 2.07] and 1.38 [1.14 – 1.61] respectively). Having an unrecognized MI increased the risk of cardiovascular mortality by two-fold among men (2.19 [1.86 – 2.91] and by approximately 30% among women (1.36 [1.03 – 1.81]), and by approximately 40-45% the risk of noncardiovascular mortality (1.46 [1.14 – 1.89] and 1.39 [1.10 – 1.75] in men and women respectively. Recognized MI was associated with an increased risk of all-cause mortality in men and women (1.67 [1.45 – 1.94] and 1.87 [1.54 – 2.28]).

Conclusions: The long-term prognosis of persons with unrecognized MI is worse than that of persons without any type of MI. In men the prognosis is as unfavorable as that of persons with recognized MI. This adverse prognosis applies to both cardiovascular mortality and noncardiovascular mortality.

P3913 Impact of positive airway pressure therapy for cardiovascular outcomes in patients with coronary artery disease and sleep-disordered breathing

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Background: The aim of this observational study is to determine whether positive airway pressure (PAP) therapy affects the long-term outcomes of patients with coronary artery disease (CAD) and sleep-disordered breathing (SDB).

Methods: We studied 1693 consecutive patients who underwent polysomnography from November 2004 to July 2011, and enrolled 150 patients with SDB (apnea-hypopnea index [AHI] ≥ 15), who had been admitted to hospital because of CAD before polysomnography. They were divided into two groups; a PAP-treated group (AHI ≥ 15 hour and treated with continuous positive airway pressure or adaptive servo ventilation) and an untreated SDB group (AHI ≥ 15 hour and untreated with PAP devices). The frequency of death and hospitalization due to cardiovascular events (acute coronary syndrome, coronary intervention, heart failure, stroke, and fatal arrhythmia) between the groups was analyzed using multivariate analysis.

Results: The mean follow-up period was 35.2±23.8 months and 26% of the patients died or were readmitted to hospital due to CVD. Kaplan-Meier survival curve indicated that event-free survival was significantly higher in the PAP-treated group than in the untreated SDB group (Figure 1). Multivariate analysis showed that the risk for death and hospitalization was significantly higher in the untreated SDB group (hazard ratio [HR], 2.62; 95% confidence interval [CI], 1.09 to 6.64; p < 0.05) than the PAP-treated group.

Conclusion: In patients with CAD and SDB, the use of PAP therapy improves long-term cardiovascular outcomes.

P3914 Time course of depressive symptoms and first coronary heart disease and stroke in older adults. A prospective observational study cohort: the Three-City study

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Objective: To prospectively investigate the association between the course of depressive symptoms over time and the occurrence of coronary heart disease (CAD) and stroke events in older adults.

Setting: The Three-City Study is a French multisite (Bordeaux (South-West), Dijon (East) and Montpellier (South East)) community-based prospective cohort. Participants: 7308 men and women aged 65 years and over with no history of CAD, stroke or dementia were recruited through the electoral rolls of these cities. Depressive symptoms assessed by the CES-D questionnaire and other risk factors were quantified at baseline and after 2 and 4 years of follow-up. Incident CHD and stroke events were adjudicated by an independent expert committee. Depressive

Conclusion: In patients with CAD and SDB, the use of PAP therapy improves long-term cardiovascular outcomes.
Prasugrel 5mg in the very elderly is non-inferior to clopidogrel 75mg. The two-dimensional strain measures of left ventricular systolic function are new independent predictors of ventricular arrhythmic events in patients with systolic heart failure.

**Results:**

- At baseline, 2 years and 4 years of follow-up, depressive symptoms (CESD score ≥16) were present in 22.7%, 18.8% and 18.9% of the participants, respectively. The corresponding rates for antidepressants use were 6.7%, 7.0%, and 7.5%. After a median follow-up of 5.25 years, 410 subjects had suffered a first CHD or stroke event including 82 fatal. After adjustment for study centre, socio-demographic characteristics and baseline conventional risk factors, the risk of CHD and stroke combined increased progressively with the percentage of time spent with depressive symptoms and was reflected in a selective association with fatal CHD events. Compared to subjects who remained free of depressive symptoms during follow-up, those with persistent depressive symptoms had an increased risk of total vascular events (HR=1.38; 95%CI: 1.07–1.80), fatal CHD and stroke combined (HR=1.52; 95% CI: 1.21–1.98), and fatal stroke (n=5; HR=5.22; 95% CI: 2.07–13.3). The risk of fatal CHD and stroke combined was even higher in depressive subjects with impaired activities of daily life (HR =1.00, 95% CI: 0.58–1.8).

**Conclusion:** The current data support a dramatic increased risk of fatal CHD and stroke events associated with the course of depressive symptoms in older adults and emphasize the need to detect depressive symptoms in that population.

**References:**

1. Lund University Hospital. Department of Cardiology. Lund, Sweden; 2. Sinai Center for Thrombosis Research, Baltimore, United States of America; 3. Uppsala Clinical Research Center, Department of Medical Sciences, Uppsala, Sweden; 4. Linköping University Hospital, Department of Cardiology, Linköping, Sweden; 5. Lund University. Dept Coagulation Medicine, Malmo, Sweden; 6. Eli Lilly and Company, Indianapolis, United States of America; 7. St Antonius Hospital, Department of Cardiology, Nieuwegein, Netherlands; 8. University of Florida College of Medicine, Center for Thorbosis Research, Jacksonville, United States of America.

**Purpose:** In the TRITON trial, prasugrel (pras) 10mg reduced ischemic events vs. clopidogrel (clop) 75mg but increased bleeding, notably in very elderly patients (VE, ≥75). Pras 5mg is suggested in VE patients to reduce the risk of bleeding, but PD data are limited. We examined PD with pras and clop in a three-period, blinded, cross-over study involving VE or non-elderly (NE, 45-65y) stable CAD patients. Assuming that VE patients on pras 5mg would show lower platelet inhibition, the primary hypothesis was that the median of pras 5mg in VE would be non-inferior to the 75th percentile of pras 10mg in the NE.

**Methods:** After a run-in on low dose aspirin, VE patients (n=73, 79±5y) and NE patients (n=82, 56±5y) were randomized to pras (5 or 10mg) or clop 75mg during three 12-day periods. PD was measured by turbidimetric aggregometry (MPA to 20 μM ADP), VerifyNow P2Y12 (VN), and VASP-PRI at pre-dose and the end of each period.

**Results:** Median MPA during pras 5mg in VE was non-inferior to the 75th percentile of pras 10mg in NE (Figure). MPA was significantly lower for pras 5mg (57±14) vs. clop (63±14) in VE, but higher than pras 10mg NE (46±12), (mean±SD, p=0.001, Figure). The antiplatelet effect based on mean MPA during pras 5mg or 10mg or clop appeared similar between cohorts. Similar PD patterns were observed with VN and VASP-PRI. Pras 5mg consistently resulted in fewer poor responders vs. clop in the VE, irrespective of definition. Higher rates of mild bleeding were seen in both VE and NE with pras 10mg, while being similar for pras 5mg vs. clop 75mg.

**Conclusions:** In patients with CAD, pras 5mg in the VE achieved pre-defined non-inferiority for PD by MPA compared to pras 10mg in NE while still providing significantly better PD and fewer poor responders than clop 75mg in VE.

**References:**

2. Lund University Hospital. Department of Cardiology. Lund, Sweden; 3. Sinai Center for Thrombosis Research, Baltimore, United States of America; 4. Uppsala Clinical Research Center, Department of Medical Sciences, Uppsala, Sweden; 5. Linköping University Hospital, Department of Cardiology, Linköping, Sweden; 6. Lund University. Dept Coagulation Medicine, Malmo, Sweden; 7. Eli Lilly and Company, Indianapolis, United States of America; 8. St Antonius Hospital, Department of Cardiology, Nieuwegein, Netherlands; 9. University of Florida College of Medicine, Center for Thorbosis Research, Jacksonville, United States of America.

**Purpose:** The current data support a dramatic increased risk of fatal CHD and stroke events associated with the course of depressive symptoms in older adults and emphasize the need to detect depressive symptoms in that population.

**Methods:** After a run-in on low dose aspirin, VE patients (n=73, 79±5y) and NE patients (n=82, 56±5y) were randomized to pras (5 or 10mg) or clop 75mg during three 12-day periods. PD was measured by turbidimetric aggregometry (MPA to 20 μM ADP), VerifyNow P2Y12 (VN), and VASP-PRI at pre-dose and the end of each period.

**Results:** Median MPA during pras 5mg in VE was non-inferior to the 75th percentile of pras 10mg in NE (Figure). MPA was significantly lower for pras 5mg (57±14) vs. clop (63±14) in VE, but higher than pras 10mg NE (46±12), (mean±SD, p=0.001, Figure). The antiplatelet effect based on mean MPA during pras 5mg or 10mg or clop appeared similar between cohorts. Similar PD patterns were observed with VN and VASP-PRI. Pras 5mg consistently resulted in fewer poor responders vs. clop in the VE, irrespective of definition. Higher rates of mild bleeding were seen in both VE and NE with pras 10mg, while being similar for pras 5mg vs. clop 75mg.

**Conclusions:** In patients with CAD, pras 5mg in the VE achieved pre-defined non-inferiority for PD by MPA compared to pras 10mg in NE while still providing significantly better PD and fewer poor responders than clop 75mg in VE.
Conclusion: The data from this study shows that quantitative LV flow vortex parameters are superior to conventional echo-Doppler measures to predict exercise capacity in patients with chronic compensated systolic heart failure.

**P3919** The incremental prognostic value of inotropic contractile reserve combined with advanced mitral regurgitation in identifying responders to cardiac resynchronization therapy

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Purpose: Inotropic contractile reserve (ICR) during dobutamine stress echocardiography differentiates the viable myocardium from scar tissue according to inotropic response. Furthermore, low dose dobutamine echocardiography is preferred in the presence of normal systolic function. The aim of this study was to identify the role of inotropic contractile reserve, in combination with the presence of functional mitral regurgitation in patient selection for cardiac resynchronization therapy (CRT) and to compare it with other echocardiographic indices used in predicting CRT response.

Methods: 42 pts referred for clinically indicated CRT were evaluated. All patients underwent low-dose dobutamine stress echo-echocardiography to assess inotropic contractile reserve, defined as an improvement of ejection fraction (EF) >5%. Mitral regurgitation (MR) severity was divided in four grades and advanced MR was defined as the presence of grade III or IV regurgitation. The interventricular mechanical delay index (by PW Doppler) and Opposing Wall Delay Index (by TDI) were used to assess intraventricular and intraventricular dysssynchrony respectively. Responders were defined by ≥15% reduction in left ventricular end systolic volume after CRT.

Results: 42 pts (mean age 68±7 years old, 28 men, NYHA III-IV) were included. The mean GRS duration was 154±95ms. During a 12-month follow up, 29 pts (69%) had responded. The ejection fraction before CRT was 24±5% and increased to 31±4% after CRT (p<0.05). The presence of ICR was the strongest predictor of response to CRT (area under the curve, 0.84 ± 0.01) compared with intraventricular dysynchrony index (area under the curve, 0.66; p<0.05) and intraventricular dysynchrony index (area under the curve, 0.74; p<0.05). The combination of ICR with the presence of advanced MR offered even greater predictive value (area under the curve, 0.89 ± 0.05).

Conclusions: Inotropic contractile reserve was a stronger predictor of CRT response than conventional and TDI indices, and its diagnostic value can be further enhanced when combined with the presence of advanced functional MR. Dobutamine stress echocardiography may play a pivotal role in identifying responders to CRT, thus avoiding ineffective interventions and reducing the cost of desynchronization management.

**P3920** Improved differential diagnosis between left ventricular non-compaction and dilated cardiomyopathy

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Introduction: Left ventricular non compaction (LVNC) is characterized by a two-layered myocardium consisting of a non-compacted inner and a compacted outer layer. Since left ventricles of many LVNC patients are dilated and exhibit poor systolic function, LVNC can be misinterpreted as dilated cardiomyopathy (DCM). This study assesses whether novel echocardiographic criteria may facilitate differential diagnosis between DCM and LVNC.

Methods: Transthoracic echocardiography was performed in 30 LVNC patients (mean age 36.3±17 years, 40 age-matched patients with DCM, and 42 age-matched controls. Maximal systolic thickness of “non-compacta” and “compacta” was measured in standard short axis views (2-D) at the apical or midventricular level in the segment with most prominent recesses (LVNC) or most prominent trabeculations (DCM and controls). The thickness of the basal septum was measured in parasternal long axis view (M-mode).

Results: LV ejection fraction was 37% (range: 10-59) in LVNC, 29% (16-51) in DCM, and 63% (range: 55-74) in controls. Maximal systolic thickness of “non-compacta” was 1.8±0.01 cm in LVNC compared to 0.4±0.02 cm in DCM (p<0.0001), and 0.2±0.01 cm in controls (p=0.0001). Maximal systolic thickness of “compacta” was lower in LVNC (0.65±0.02 cm) compared to DCM (1.0±0.02 cm; p<0.0001) and controls (1.1±0.03 cm; p<0.0001). Maximal systolic thickness of “compacta” was ≥8.2 mm (range: 3.5-8.2) in LVNC versus ≥8.5 mm (range: 8.5-14.0; p<0.0001) in DCM and >8.6 mm (range: 8.6-15.0; p<0.0001) in controls. The ratio of maximal systolic thickness of the indexed basal septum to that of the “compacta” was ≥0.64/m² (range 0.64-1.90) in LVNC versus ≥0.61/m² (range 0.29-0.61) in DCM and >0.57/m² (range 0.28-0.57) in controls.

Conclusion: Maximal systolic “compacta” thickness >8.2 mm and a ratio of indexed septal wall thickness to “compacta” thickness >0.64/m² is specific for LVNC. This observation may be particularly useful in patients with dilated ventricles and facilitate the differential diagnosis between LVNC and DCM.

**P3921** Visual assessment of apical rocking predicts response and long-term survival following cardiac resynchronization therapy

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Purpose: Apical rocking can predict reverse remodeling and survival in cardiac resynchronization therapy (CRT) candidates.

Methods: A total of 201 patients eligible for CRT (63±11 years, ejection fraction 26±6%) underwent standard echocardiographic examination before and 12±2 months after device implantation. Three blinded physicians were asked to assign response to CRT (yes/no) by visually assessing the presence of apical rocking and extend and localize of infarct scar. Response was defined as LV end-systolic volume decrease >15%. Patients were followed for an average period of 37±19 months for the occurrence of cardiac death.

Results: Visually assessed apical rocking predicted reverse remodeling with a sensitivity, specificity and accuracy of 95, 85, and 90%, respectively. Physicians’ prediction of CRT response integrating apical rocking and scar burden resulted in a sensitivity, specificity and accuracy of 95, 85, and 90%, respectively. When corrected by CRT, visually detected apical rocking was the only parameter associated with favorable outcome, whereas worse functional class, a high scar burden (>6 segments) and atrial fibrillation were associated with poorer survival (Figure). Baseline LV ejection fraction and GRD duration did not predict outcome.

Conclusions: Simple visual assessment of apical rocking is a robust predictor of response and long-term survival after CRT. In patients with heart failure of ischemic origin, visual assessment of scar burden further enhances predictive power of visible LV dysynchrony.
value on the strain curve during the entire cardiac cycle. Values obtained from each of 18 LV segments were averaged.

**Results:** Median plasma NTproBNP levels (IQ range) were 164 ng/l (95-268) in patients with no evidence of cardiac dysfunction, 414 ng/l (143-867) in grey cases and 1627 ng/l (868-2837) for definite HFNEF. Mean LVEF was 58% in each subgroup. Patients with HFNEF were older (78 years) and had more dyspnea at rest, lower NYHA functional class, more history of heart failure, more prevalent atrial fibrillation (AF) and more AF-related complications compared to patients with MI. Additionally, patients with NT-proBNP levels ≥350 ng/l had more heart failure symptoms, higher LVEF, and were more likely to show dyssynchrony without significant discoordination compared to those with NT-proBNP levels <350 ng/l.

**Conclusions:** NT-proBNP levels ≥350 ng/l are associated with increased risk of heart failure and increased levels of vascular oxidative stress, as assessed by serum L-arginine/ADMA ratio levels. Further experimental studies are needed to explore the relationship between L-arginine metabolism pathways, endothelial dysfunction and mechanisms of leukocyte telomere shortening.

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**Table 1. Comparisons of left ventricular discoordination and dyssynchrony between patients with different characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Narrow QRS</th>
<th>Wide QRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrow QRS (%)</td>
<td>156±22</td>
<td>162±23</td>
</tr>
<tr>
<td>Wide QRS (%)</td>
<td>3.2±0.5</td>
<td>4.1±0.7</td>
</tr>
<tr>
<td>Non-LBBB (%)</td>
<td>10.3±1.5</td>
<td>10.8±2.0</td>
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<tr>
<td>LBBB (%)</td>
<td>10.1±1.0</td>
<td>10.0±1.0</td>
</tr>
<tr>
<td>PAC (%)</td>
<td>3.1±0.3</td>
<td>3.2±0.3</td>
</tr>
<tr>
<td>RDI (%)</td>
<td>4.1±0.6</td>
<td>5.8±1.3</td>
</tr>
<tr>
<td>GLS (%)</td>
<td>4.5±1.0</td>
<td>4.7±1.0</td>
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<tr>
<td>LVEF (%)</td>
<td>58.6±2.1</td>
<td>57.9±2.2</td>
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<td>LVEFSD (%)</td>
<td>18.6±3.4</td>
<td>19.3±3.5</td>
</tr>
<tr>
<td>LVEFSD (%)</td>
<td>6.6±1.0</td>
<td>6.1±1.0</td>
</tr>
</tbody>
</table>

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**Abstract P3923**

**Comparison of left ventricular discoordination and dyssynchrony assessment by radial strain imaging in cardiac resynchronization therapy**

Y.H. Chan, L.S. Wu, Y.H. Yeh, C.L. Wang, Y.J. Ho, L.A. Hsu, C.T. Kuo on behalf of First Division of Cardiovascular Department, Chang Gung Memorial Hospital, Linkou. Chang Gung Memorial Hospital, Taoyuan, Taiwan.

**Background:** Patients with nonischemic etiology, left bundle-branch block (LBBB) and CRT duration ≥150 ms are more likely to benefit from cardiac resynchronization therapy (CRT) than those without. This study aimed to compare mechanical discoordination and dyssynchrony in CRT candidates.

**Methods:** Speckle-tracking strain imaging was performed in 120 CRT candidates and 60 patients with LVEF ≤35% and CRT duration ≤120 ms. CRT candidates were divided into subgroups according to the etiology of heart failure (ischemic vs nonischemic), RS duration (≤150 ms vs ≤150 ms) and CRT duration (≤150 ms vs ≤150 ms). Dyssynchrony indices based on time-to-peak radial strain of anteroseptal and posterior walls (AS-P delay) and standard deviation of time-to-peak radial strain (RS-SD) were measured. Discoordination was indexed using the mid-ventricular radial discoordination index (RDI-M).

**Results:** RDI-M could distinguish between patients in the narrow and wide ORS groups and between subgroups with and without favorable characteristics. Compared to ischemic candidates, nonischemic candidates had greater myocardial thinning (P<0.003), smaller myocardial thickening (P<0.009) and a greater RDI-M (P=0.003). In contrast, AS-P delay and RS-SD failed to demonstrate significant differences between ischemic and nonischemic subgroups. CRT candidates with ischemic etiology were more likely to show dyssynchrony without significant discoordination than nonischemic candidates.

**Conclusions:** Mechanical discoordination performed better than dyssynchrony in differentiating CRT candidates with and without favorable characteristics.

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**THE ENDOTHELIUM: KEY PLAYER IN VASCULAR CONTROL**

**3957 Reduced leukocyte telomere length are associated with increased levels of vascular oxidative stress in patients with acute myocardial infarction**

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**Purpose:** Asymmetric dimethylarginine (ADMA), competes with L-arginine to inhibit NO synthesis (NOS), leading to a decreased NO bioavailability, increasing vascular oxidative stress and endothelial dysfunction. Recent data suggest that reduced leukocyte telomere length (LTL) could be associated with increased risk for acute myocardial infarction (MI). The aim of our study was to analyse the relationship between LTL and ADMA, as a biomarker of oxidative stress, in patients with acute MI.

**Methods:** Blood samples from 33 consecutive patients hospitalized <24 hours after symptom onset for acute MI were taken on admission. Serum levels of ADMA, SMDA (its biologically inactive symmetrical stereoisomer and L-arginine) were determined using high-performance liquid chromatography. LTL was assessed by extraction of leukocyte DNA from venous blood samples and performing real time PCR. The L-arginine/ADMA ratio was used as a biomarker of vascular oxidative stress and endothelial dysfunction. Patients from the lowest L-arginine/ADMA tertile were compared with patients from the higher L-arginine/ADMA tertiles.

**Results:** Demographic data, chronic treatments, cardiovascular risk factors and history were similar for the 2 groups. Strikingly, in patients with the lower L-arginine/ADMA levels, CRT was markedly reduced when compared with the highest L-arg/ADMA levels (1.15±0.27 vs 1.91±0.40; p<0.005). LTL was negatively correlated with age (r=-0.356, p=0.004). Moreover, a trend for a positive correlation between LTL and L-arginine/ADMA ratio was noted (r=0.339, p=0.053) but not with SMDA, (r=0.069, p=0.698).

**Conclusions:** Our study showed that, in MI patients, reduced LTL was associated with increased levels of vascular oxidative stress, as assessed by serum L-arginine/ADMA ratio levels. Further experimental studies are now needed to explore the relationship between L-arginine metabolism pathways, endothelial dysfunction and mechanisms of leukocyte telomere shortening.

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**3958 Circulating plasma free heme levels correlate with endothelial injury and atherosclerotic lesions extent in patients with stable coronary artery disease**

N. Amabile1, C. Guerin1, C. Cassains1, O. Blanc-Brude2, C.M. Boulanger2

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**Purpose:** Spontaneous hemolysis is associated with plasma free heme release in that could increase oxidative stress phenomenon and enhance vascular cellular damage, leading to endothelial dysfunction and ultimately atherosclerosis. We investigated if free heme release could be related to endothelial injury and atherosclerotic lesion extent in patients with cardiovascular risk factors (CRF).

**Methods:** Patients with cardiovascular risk factors who underwent coronary angiography for suspected stable coronary artery disease were eligible for inclusion. Levels of endothelial (CD144+ EMPs), erythrocytes (CD235a + RBCs), platelets (CD41+ PMPs) and leukocytes-derived microparticles (CD11a + LMPs) were measured by flow cytometry methods on free platelets plasma samples. Levels of circulating free heme (CFH) were analyzed by absorption spectro-photometry methods. Significant CAD was angiographically defined as presence of at least 1 stenosis with ≥50% luminal diameter narrowing. The atherosclerotic lesions extent was evaluated by the Gensini score calculation.

**Results:** A total of n=97 subjects (63.6±1.1% 78 male gender/32% diabetes) fulfilled the inclusion criteria. These patients had significantly higher levels of CFH compared to healthy subjects without CRF. We observed higher levels of CFH in diabetic patients compared to non-diabetic subjects (10.2±1.0 vs 8.2±0.5 AU, p=0.03), whereas no significant influence of other risk factor (hypertension, dyslipidemia, active smoking) was noted. Moreover, CFH levels were correlated with CD144+ EMPs (r=0.26, p=0.01), suggesting a potential link between hemolysis and endothelial dysfunction.

**Significant CAD was diagnosed in n=71 patients in whom the Gensini score was significantly correlated with CFH levels (r=0.44, p=0.001), as well as LMPs (r=0.31, p=0.02) and fasting glucose levels (r=0.49, p=0.001). Multivariate regression analysis revealed that CFH levels were independent related to atherosclerotic lesions extent (p=0.017) after adjustment for other confounding factors.

**Conclusions:** Increases in circulating free heme levels are associated with endothelial injury in patients with cardiovascular risk factors and atherosclerotic lesions severity in stable CAD subjects. These results suggest that CFH might influence coronary artery disease development.

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**3959 Changes in blood flow determine endothelial vasomotor responses: insight into the meaning of flow-mediated constriction and dilation**

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**Introduction:** Flow-mediated dilation (FMD) is an accepted parameter ofendo-
The endothelium: key player in vascular control

Epigenetic regulation of cell adhesion and protection against stroke through preservation of the (endothelial) reactivity to supranormal increases in shear stress (endothelial tone in resting conditions as well as during reactive hyperemia).

Conclusions:
Arterial blood flow and shear stress are important determinants of FMD. In patients with PAD, there was a strong inverse correlation between resting radial artery diameter and FMD (r = -0.27, p < 0.0001). After 4.5 minutes of distal ischemia, the release of the pneumatic cuff caused a reac-
tion of the endothelium to supranormal increases in shear stress (endothelial reactivity, or reactivity). From this perspective, a lower FMD in subjects with larger conduit arteries may not be representative of abnormal endothelial function but rather of an increased basal endothelial activity.

Epigenetic regulation of cell adhesion and communication by enhancer of zeste homolog 2 in human endothelial cells

Objective:
Epigenetic modifications such as DNA and histone methylation have long-term effects on gene expression. The histone methyltransferase Enhancer of zeste homolog 2 (Ezh2) mediates trimethylation of lysine 27 in histone 3 (H3K27me3) which acts as a repressive epigenetic mark. Previous studies demonstrated an essential role for Ezh2 in different differentiation processes of human stem cells. In differentiated endothelial cells, however, information about the func-
tion of Ezh2 is missing. Therefore, the aim of our present study was to identify Ezh2 target genes in endothelial cells.

Methods and Results:
Whole genome mRNA expression arrays identified 964 genes that were regulated by more than twofold after knock down of Ezh2 and ii) association with blood flow caused by the inflation of the pneumatic cuff (r = 0.26, P < 0.0001). After 4.5 minutes of distal ischemia, the release of the pneumatic cuff caused a reactive hyperemia (302±238% compared to baseline flow) and a subsequent FMD (r = 0.19, P < 0.0001) for the correlation between increase in arterial diameter and the increase in arterial blood flow.

Conclusions:
Arterial blood flow and shear stress are important determinants of endothelial tone in resting conditions as well as during reactive hyperemia. By measuring the change in arterial diameter in the setting of reduced shear stress, L-FMC quantifies "resting" endothelial function. In contrast, FMD reflects the (endothelial) reactivity to supranormal increases in shear stress (endothelial reactivity, or reactivity). From this perspective, a lower FMD in subjects with larger conduit arteries may not be representative of abnormal endothelial function but rather of an increased basal endothelial activity.

The effects of AdVEGF-B and AdVEGF-D on angiogenesis and arteriogenesis in a novel porcine model of percutaneous bottleneck stent induced chronic myocardial ischemia and test adenoviral (Ad) VEGF-D and VEGF-B gene therapy in this model.

Methods: Ischemia was induced by restricting coronary blood flow in either proximal left circumflex artery (LCX) or left anterior descending artery (LAD) by installing a bare metal stent covered by a bottleneck shaped tube in domestic pigs. One week after the stent placement, gene transfer was conducted. Collateral vessel formation, ejection fraction of adenoviral VEGF-B and VEGF-D and myocardial microvascular resistance were assessed using coronary angiography, left ventricle cineangiography, modified Miles assay, myocardial contrast echocardiography (MCE) and index of myocardial resistance (IMR) measurements, respectively.

Results: Notable collateral vessel formation to LCX and LAD area in the respective models was observed. Ejection fraction during stress decreased from 80% to 66% and 46% in the LCX and LAD models, respectively. After 4.5 minutes of ischemia, myocardial perfusion and blood flow would impact the vascular response to reactive hyperemia and myocardial edema six days after gene transfer, but the effects were disappeared four weeks after gene transfer. The effects of adenoviral VEGF-B and VEGF-D gene transfers on blood vessel growth in the ischemic heart will be presented in detail in the congress.

Conclusions: We have established a novel porcine model of chronic myocardial ischemia, which is minimally invasive, repeatable, and which offers multiple clinically relevant endpoints. The LCX model, which is not as severe as the LAD model, can be applied to studies concerning collateral vessel formation while the more severe LAD model can be applied to study treatments for ischemic cardiomyopathy.

Protection against stroke through preservation of vascular integrity by angioptelin-like 4 (ANGPTL4)

Aims: Timely recanalization of the occluded artery is the treatment for ischemic stroke, but has limited application. We demonstrated that ANGPTL4 has vasculoprotective effects in myocardial infarction by counteracting VEGF-induced permeability. Given the impact of vascular leakage and edema formation in tissue damage during stroke, preserving vascular integrity represents a pertinent strategy for brain protection. Therefore we hypothesized that ANGPTL4 might exert cerebral protection in stroke.

Methods and Results: In a mouse model of ischemic stroke, with 1 hour is-
chemia followed by 24 hour reperfusion, injection of ANGPTL4 at ischemia led to a decreased infarct size, as assessed by TTC staining (p < 0.0008) and cerebral MRI (p = 0.003). Brain edema was decreased in the ANGPTL4 treated group (p < 0.0002). Using PECAM staining, we demonstrated that vascular network was pre-
served in ANGPTL4-treated mice (vascular density p < 0.0007 and branching points p = 0.002). We then assessed integrity of tight and adherens junctions us-
ing VE-cadherin and Claudin-5 immunostainings. We showed a significant in-
crease in VE-cadherin and Claudin 5 areas (normalized to endothelial cell sur-
face) in ANGPTL4-treated mice. Thus ANGPTL4 protects from global vasu-
lar damage, but also specifically protects from ischemia-induced junctions dis-
ruption. ANGPTL4 protective effect on junctions was further assessed in vitro using microvascular endothelial cells (HDMEC) treated with VEGF+ANGPTL4 and stained with VE-Cadherin antibody. The straight and tight VE-Cadherin junc-
tions were observed by PECAM staining. We showed a significantly decreased recruitment of phospho-VEK in infarcted hemispheres of ANGPTL4-treated mice. Thus ANGPTL4 counter-
acts VEGFR2-induced Src signaling and protects VE-Cadherin junctions from Src dependent disassembly. Moreover, ANGPTL4 protected neuronal loss after stroke, as assessed by the increased number of NeuN-positive cells (neurons) in treated mice (p < 0.001). Finally, mouse behavior was also significantly improved in treated mice (p < 0.01).

Conclusion: ANGPTL4 treatment counteracts the loss of vascular integrity in a mouse model of ischemic stroke, by restricting Src kinase recruitment down-
stream VEGFR2. Consequently, ANGPTL4 reduces edema, infarct size, neuronal loss and finally improves mouse behavior. These results show that ANGPTL4 is a relevant target for vasculoprotection, thus conferring cerebral protection during stroke.
A national, multicentre, randomized controlled trial of Valsartan suppresses cardiovascular events in ofVIPER-BP intervention (adjusted RR 1.18, 95% CI 1.07 – 1.31, p=0.001). BP target of 29% (adjusted RR 1.31, 95% CI 1.11 – 1.54, p=0.001). At the higher, historical versus 10.4 (95% CI -11.7 to -9.1)/5.6 (95% CI - 4.7 to -6.4) mmHg. Accordingly, (mainly valsartan-based) therapy, and the rest triple anti-hypertensive therapy. treatment (initial angiotensin receptor blocker (ARB) mono- or two forms of single pill ARB combination therapy) and computer assisted intensified follow-up and treat- ment titration. The primary endpoint was individualized BP control at 26 weeks. Results: A total of 495 (94%) and 921 (90%) actively treated UC and VIPER-BP patients respectively were randomized to treatment and followed up for the pre- dicted 26 week (for UC) and 24 week (for BP) treatment period. The individualised target BPs in primary care, lower targets required by guidelines for high risk patients are cultured/ BP management improves the BP profile of patients with persistently high and reflects real-world practice. Although effective pharmacotherapy with struc- tured BP management improves the BP profile of patients with persistently high BPs in primary care, lower targets required by guidelines for high risk patients are rarely achieved.

Antihypertensive and laxative effects by inhibition of NHE3-mediated sodium absorption in the gut

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Purpose: High intestinal sodium absorption is one important mechanism of hy- pertension and constipation. The sodium-proton-exchanger (NHE3) is an im- portant mediator of sodium absorption in the gut. Insulin stimulates the NHE3-exchanger. We used senescent lean hypertensive rats (SHR-lean) and a hyper- tensive, obese and hyperinsulinemic rat strain (crossbreeding leptin receptor de- ficient hypertensive rats, SHR-ob), and treated them orally with a non-absorbable specific NHE3-inhibitor.

Methods: Twenty-six week old senescent SHR-lean were randomized in 2 groups (n=14/group): placebo (PLAC) and NHE3-inhibitor SAR (1mg/kg/d) in chow, treated for 14 weeks. Eight weeks old SHR-ob were randomized in two groups: PLAC (n=7) and SAR (n=8), treated for 6 weeks. Water and sodium content in the feces were determined via flame photometric analysis, for 32 years.

Results: SAR treatment resulted in a dose dependent increase of feces sodium and water content in normotensive Sprague Dawley rats. In senescent SHR-lean, inhibition of intestinal NHE3 increased sodium (33.5±3.4 mmol/L vs. 20.2±2.2 mmol/L, p<0.01) and water content (58% vs. 42% in PLAC control, p<0.01) in the feces and reduced sodium blood pressure compared to senescent SHR-lean. Body weight, serum insulin or cholesterol levels were not modified by SAR in SHR-ob.

Conclusion: Reduction of intestinal sodium absorption by selective NHE3- inhibition in the gut reduces high blood pressure and increases feces water ex-

Predictive factors of adherence in uncontrolled hypertensive patients in France: results of the observational real life survey HBP-ADHERENCE

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Purpose: Despite antihypertensive treatment, the proportion of uncontrolled hypo- tertensive patients remains high and the non adherence to treatment is a major issue. One of the aims of this study was to determine the predictive factors of anti- hypertensive medication adherence in uncontrolled hypertensive patients treated by general practitioners in France.

Methods: HBP-ADHERENCE observational study was conducted in France from March to September 2011. A population of 5660 hypertensive patients was in- cluded by 1049 French general practitioners. Hypertensive patients whose blood pressure was not controlled with at least two antihypertensive drugs were in- cluded. Adherence was determined according to a validated questionnaire. Com- parative analyses were performed on two subgroups of patients: “adherent or minor non-adherent” versus “major non-adherent”.

Results: Mean systolic and diastolic blood pressure (SP/DPB) were 157±11/91±8 mmHg. The majority of patients (60%) were over 60 years old and nearly 40% were women. Patients were classified as “major non-adherent” in 7% of cases. Age and sex were neither predictive factors of adherence. Major non- adherent patients had a significantly higher number of drugs prescribed (5.4±2.6 versus 4.6±2.4 p<0.0001), larger number of daily medication intakes (3.6±2.9 versus 3.0±2.3, p<0.0001) and less knowledge about their treatments (73.7% versus 88% or more p<0.0001) than adherent or minor non-adherent patients. Multi- variate analysis, independent factors strongly associated with risk of major non- adherence were: OR (95% CI); fear of adverse effects (2.7, 1.23-4.34), presence of at least one symptom (1.93, 1.59-2.45), sedentarity (1.33, 1.0, 1.76), exces- sive alcohol intake (1.65, 1.24-2.20). The regular practice of home blood pres- sure measurement was the only factor inversely correlated to the risk of major non-adherence (0.64, 0.48-0.86).

Conclusion: In this real life study, we identified several modifiable factors to pre- dict risk of non-adherence in uncontrolled hypertensive patients. Therapeutic ed- ucation focusing on the expected benefits of antihypertensive drugs, their mech- anisms of action and their adverse effects, as well as a wider use of long acting fixed-dose combinations would improve long-term effective care of hypertensive patients.

Valsartan suppresses cardiovascular events in hypertensive subjects with diabetes mellitus (DM) comparable to those with impaired glucose tolerance (IGT)

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Purpose: The randomized Nagoya Heart Study has demonstrated that com- parable cardiovascular outcomes were comparable between the valsartan- and amlodipine-based treatments in Japanese hypertensive patients with glucose in- tolerance. The present subanalysis aimed to clarify whether or not the effects of those two drugs differ depending on the presence of glucose intolerance (diabetes mellitus: DM vs. impaired glucose tolerance: IGT).

Methods: Treatment: effects were evaluated among 942 hypertensive subjects with DM (valsartan, N=471; amlodipine, N=472) and 208 hypertensive subjects with IGT (valsartan, N=471; amlodipine, N=472). The primary outcome was a new onset DM from IGT was less in the valsartan-based treatment than in the amlodipine-based treatment, more cardiovascular events occurred in DM com- pared to IGT, non adherence were (OR, 95% CI): fear of adverse effects (2.76, 1.23-3.43), presence of at least one symptom (1.93, 1.59-2.45), sedentarity (1.33, 1.0, 1.76), exces- sive alcohol intake (1.65, 1.24-2.20). The regular practice of home blood pres- sure measurement was the only factor inversely correlated to the risk of major non-adherence (0.64, 0.48-0.86).

Results: Among hypertensive subjects with DM, 101 events occurred, against only 9 among those with IGT (hazard ratio: 2.48 [95% CI: 1.27-4.82]; P<0.007). When subjects who remained IGT was used as a reference group, the hazard ratio was 1.39 (P=0.6156) in the new onset DM group and 2.83 (P=0.020) in the DM group. In the amlodipine-based treatment, the event rate was higher among DM subjects compared to IGT subjects (hazard ratio: 3.05 [95% CI: 2.12-12.10]; P=0.020). Similar trend was observed in the valsartan-based treatment, but it was not statistically significant (hazard ratio: 1.79 [95% CI: 0.79-4.07]; P=0.166). The creatinine value of new onset DM from IGT was lower in the valsartan-based treatment (N=33) than in the amlodipine-based treatment (N=43), although it was not statistically significant (hazard ratio: 3.05 [95% CI: 0.52-1.08]; P=0.125).

Conclusions: Comparative cardiovascular events increased in the order of IGT, new onset DM from IGT, new compared to senescent DM in Japanese hypertensive subjects. In the amlodipine-based treatment, more cardiovascular events occurred in DM com- pared to IGT, but not in the valsartan-based treatment. Moreover, the number of new onset DM from IGT was less in the valsartan-based treatment than in the
Impact of intensive blood pressure lowering therapy on left atrial volume and function and the incidence of first atrial fibrillation in elderly hypertensive patients with preserved systolic function

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Purpose: The risk of atrial fibrillation (AF) associated with left atrial (LA) remodeling is increasing in elderly hypertension (HTN). Intensive BP lowering therapy would have a beneficial effect on LA structure and function and decreases the incidence of first AF in elderly HTN.

Methods: We studied 240 subjects ≥65 years, who were divided into 4 groups by mean office BP for past 2 years; normal (n=73, 75±5 yrs, 37 men), intensive controlled HTN (systolic BP-130 and diastolic BP<-80mmHg, n=74, 74±4 yrs, 42 men), poor controlled HTN (systolic BP-140 and diastolic BP>90, n=141, 74±5 yrs, 53 men) and good controlled HTN (130≤sBP≤140/90, n=74, 75±4 yrs, 21 men). LA volume, emptying function (EF), strain rate (SR) and strain were measured by speckle tracking echocardiography at baseline and after 2 years. Results: There was no difference in LV ejection fraction among 4 groups. LA volume, EF, SR and strain in intensive controlled HTN were more preserved and comparable to normal including diastolic function at baseline and after 2 years. The incidence of first AF was significantly lower in intensive controlled HTN for 2 years.

Table 1. parameters at baseline

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Intensive HTN</th>
<th>Good HTN</th>
<th>Poor HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>126±8</td>
<td>126±8</td>
<td>126±8</td>
<td>126±8</td>
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<tr>
<td>Diastolic</td>
<td>75±5</td>
<td>75±5</td>
<td>75±5</td>
<td>75±5</td>
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<tr>
<td>LA dimension, mm</td>
<td>39±5</td>
<td>40±5</td>
<td>41±6</td>
<td>45±6</td>
</tr>
<tr>
<td>LA active EF%</td>
<td>45±6</td>
<td>45±6</td>
<td>45±6</td>
<td>33±5</td>
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<tr>
<td>LA passive EF%</td>
<td>22±8</td>
<td>20±7</td>
<td>17±6</td>
<td>14±5</td>
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<tr>
<td>LA peak strain</td>
<td>30±8</td>
<td>30±7</td>
<td>28±7</td>
<td>22±5</td>
</tr>
<tr>
<td>SR-systole, s-1</td>
<td>1.2±0.3</td>
<td>1.1±0.3</td>
<td>1.1±0.3</td>
<td>1.0±0.4</td>
</tr>
<tr>
<td>SR-early diastolic, s-1</td>
<td>-1.0±0.3</td>
<td>-1.0±0.3</td>
<td>-0.8±0.3</td>
<td>-0.8±0.3</td>
</tr>
<tr>
<td>LA atrial contraction, s-1</td>
<td>-1.4±0.4</td>
<td>-1.4±0.4</td>
<td>-1.4±0.5</td>
<td>-1.0±0.4</td>
</tr>
</tbody>
</table>

*p<0.05 vs. normal, †p<0.05 vs. intensive HTN, ‡p<0.05 vs. good HTN.

Conclusion: LA structure and function were preserved in intensive controlled HTN associated with preserved diastolic function and comparable to normal. Intensive BP lowering therapy had a beneficial effect on LA structure and function and would be recommended to prevent LA remodeling and first AF in elderly HTN.

4372 Pilot analysis of the effect of the SGLT2 inhibitor dapagliflozin on blood pressure in patients with type 2 diabetes mellitus: a pooled analysis of placebo controlled trials

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Purpose: Obesity and hypertension are common comorbidities in patients with type 2 diabetes mellitus (T2DM). The glucoretic mechanism of dapagliflozin (DAPA), a selective sodium-glucose co-transporter 2 (SGLT2) inhibitor, is associated with improvements in hyperglycaemia and weight loss. A modest mean reduction in blood pressure (BP) has been observed in development studies, potentially as a result of osmotic diuresis, and to some extent weight loss. The aim of this post-hoc analysis is to further characterise the BP effects of DAPA in patients with T2DM.

Methods: Safety data were pooled from 12 placebo (PBO) controlled phase IIb and III studies. Patients with T2DM (N=4545) received DAPA (2.5, 5 or 10 mg) or PBO daily for 12–24 weeks (wks). Background antihypertensive therapy was not controlled.

Results: Greater mean reductions from baseline (BL) BP levels were observed at each time point measured across the DAPA groups compared with PBO for systolic BP (sBP) and diastolic BP (dBP) (Figure). At 24 wks there was a mean change from BL in heart rate of −0.4 to −1.1 beats per min (BPM) across the DAPA groups and an increase of 0.5 BPM with PBO. AEs of hypertension/hypovolaemia were slightly more frequent with DAPA (0.6–1.2%) versus PBO (0.4%) none of which were serious or resulted in discontinuation. The proportion of patients with measured orthostatic hypotension at any visit during treatment was 10.0–12.5% with DAPA and 9.2% with PBO.

Conclusions: DAPA is associated with modest mean reductions in sBP and dBP in patients with T2DM, with no increased risk of orthostatic hypotension and without any clinically relevant changes in heart rate. These post-hoc observations are intriguing and further studies will be needed to evaluate potential clinical benefit in hypertensive patients.

4377 Exercise related out-of-hospital cardiac arrest: incidence, prognosis, and prevention of sudden death

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Purpose: Although regular physical activity has beneficial cardiovascular effects, exercise can trigger an acute cardiac event. We aimed to determine the incidence of exercise related out-of-hospital cardiac arrest (OHCA) and whether exercise-related OHCAs are associated with higher survival rates than non-exercise-related OHCAs in persons aged ≥35 years.

Methods: We analyzed all OHCA cases prospectively collected from January 2006 to January 2009. The relation between exercise during or within 1 hour before OHCA and outcome was analyzed using multivariable logistic regression, adjusting for age, gender, public location, bystander witnessed, bystander cardiopulmonary resuscitation (CPR), automated external defibrillator (AED) use and shockable initial rhythm. Incidence is shown per 100,000 person-years.

Results: Of 2517 OHCA, 145 (5.8%) were exercise-related, of whom 7 were ≤35 years. Most patients were men (93.1% and 85.7%, respectively). The incidence of exercise-related OHCA was 2.0 in all ages and 0.2 in those <35 years. Survival after exercise-related OHCA was distinctly better than after non-exercise-related OHCA (44.8% vs. 15.4%) (unadjusted odds ratio 4.13; 95%CI 2.93-5.62; *P=0.001), even after adjustment for other prognostic factors (odds ratio 1.57; 95%CI 1.04-2.37; *P=0.03). Patients <35 years did not benefit from exercise; survival was 33.3% versus 34.5%, respectively (adjusted odds ratio 0.47; 95%CI 0.04-5.37; *P=0.54). In hospital treatment did not differ between groups.

Conclusions: Exercise-related OHCA has a low incidence, particularly in the young and predominantly affects men. Cardiac arrests occurring during or shortly after exercise carry a markedly better prognosis than cardiac arrests that are not exercise-related in persons older than 35 years.

4378 Costs of cardiovascular screening with ECG in young athletes in Switzerland

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Purpose: Adding ECG to cardiovascular screening in young athletes remains a controversial issue. One of the reasons refers to costs of the screening program and the subsequent cardiac examinations generated mainly by the false positive ECG. The aim of this study was to assess the total costs of a program of cardiovascular screening with ECG in young athletes in Switzerland using basically the 2010 recommendations of the European Society of Cardiology (ESC) for interpretation of ECG in athletes.

Methods: In this observational prospective study, competitive athletes from 14 to 35 years were examined following the 2005 ESC proposal. ECG was interpreted based on the ESC 2010 recommendations (adapte). Further examinations were proposed in cases of positive findings. The costs of the screening and of all subsequent examinations were calculated for each athlete according to the Swiss medical rates. We present the intermediate results of this study.

Results: Of 2011 to 2012, 920 athletes were examined. Mean age was 19.9±6.5 years, 75% were men. Football (35%) and ice hockey (12%) were the sports most often represented. Mean weekly training’s hours were 7.9±4.8 for a
Concentric remodelling of the right ventricle in African football players

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Purpose: We have previously shown that male Caucasian athletes have a larger increase of both LV and RV size than Africans athletes. African athletes, however, had similar LV mass but markedly more concentric remodelled LV than the Caucasian athletes. Thus, the aim of this study was to investigate if a similar remodelling between black and white athletes is present in the RV.

Method: As a part of the mandatory heart screening, 555 male elite football players (509 Caucasians and 46 Africans) and 46 Caucasian controls were examined. RV and diastolic middle diameter (RVD2) were measured from a RV focused apical 4 chamber view. Measurements of RV free wall thickness (RWTW) in end diastole were performed by a subcostal view. Relative wall thickness on the right side (RVRWT) was calculated by dividing RWTW with RVD2 multiplied with two. Body mass index (BMI) and body surface area (BSA) were calculated, and all echo measurements were performed blinded.

Results: Concentric remodelling of the RV free wall thickness (RVRWT) was significantly more pronounced in the Africans than the white athletes.

Conclusions: Our results indicate that RV free wall thickness in athletes exhibited the same pattern as LV wall thickness. Moreover, and similar to the LV, black athletes had a significantly more pronounced concentric remodelled RV than the white athletes.

Prevalence of significant ECG abnormalities in elite Australian athletes

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Purpose: The effectiveness and cost-effectiveness of an athlete screening program is dependent on the prevalence of abnormalities on screening tests such as electrocardiography (ECG). As the prevalence of ECG abnormalities in athletes is unknown, our aim was to evaluate the frequency of ECG abnormalities in a cohort of elite Australian athletes.

Methods: A total of 450 elite Australian athletes (age 16-35) competing at national and international level underwent 12-lead ECG examination. They were predominantly male \( (n=413, 92\%) \) with a mean age 20.9 ± 4.8 years; mean hours training per week 15.0 ± 7.8 from a range of endurance (road cycling n=48; rowing n=23; race walking n=2) and non-endurance sports (including football n=324; basketball n=10 and basketball n=15). ECGs were evaluated using criteria in the ESC recommendations for athlete ECG interpretation (2010).

Results: Group 1 (training related) ECG changes were more common in endurance versus non-endurance athletes (57% vs. 16%, \( p<0.005 \)); left ventricular hypertrophy on voltage criteria (45% vs. 30%, \( p<0.001 \)); incomplete RBBB (26% vs. 17%, \( p=0.001 \)) and early repolarisation (64% vs. 55%, \( p<0.005 \)). PR interval \( <0.25 \) was seen in both groups (5.5% vs. 6.5%, \( p=0.5 \)). Group 2 (uncommon and training unrelated) ECG changes were seen in 29 (6.4%) of the athletes and were also more common in endurance athletes (8.2% vs. 6.1%, \( p<0.005 \)); right axis deviation (OR axis \( \geq 105^\circ \)) in 11 (2.4%); right ventricular hypertrophy (RV1+SV2 ≥15mm) in 8 (1.7%); abnormal T-wave inversion in 7 (1.5%); RBBB in 2 (0.4%); left anterior fascicular block in 3 (0.6%); ST-segment depression in 1 (0.6%) and left atrial enlargement in 3 (0.6%). There were no cases of pre-excitation, long or short QTc, pathological Q waves or Brugada-like ECGs. No athlete with Group 2 ECG changes had features of underlying structural heart disease on further evaluation with echocardiography.

Conclusions: In elite Australian athletes, Type 1 or training related ECG changes are common and more prevalent in endurance athletes. The prevalence of Type 2 ECG changes requiring further investigation is low, possibly due to ‘self selection’ in the elite cohort. While ECG abnormalities are common in endurance athletes they rarely reflect structural disease. Further evaluation in a sub-elite cohort is warranted.
based on exercise-stress test and cardiovascular risk factors can be used to assess more accurately the risk of sudden cardiac death (SCD).

**Methods:** A total of 3282 randomly selected men aged 42-60 from eastern Finland were included in this population-based follow-up study (mean follow-up time was 19 years). Exercise stress test was performed and information on risk factors was collected. SCD was defined as cardiac deaths that occurred 24 hours after onset of symptoms. The population was divided into low and high CRF (MET 8 as cut-off point) and analyzed with dichotomously divided risk factors. The risk factors included age, sex, smoking, hypertension, diabetes mellitus, atrial fibrillation, and selective coronary angiography. According to the Smoking History and Western Becking Score (MET 8 as cut-off point), the risk factors were divided into low and high CRF groups. The high CRF group was characterized by a low smoking history and a score of less than 8 METs. The low CRF group was characterized by a high smoking history and a score of more than 8 METs.

**Results:** Low CRF combined with all measured risk factors was associated with a higher risk of SCD (4.9%). The highest risk factor for SCD was low CRF with a smoking history of more than 10 packyears, which increased the risk of SCD (4.9%).

**Conclusion:** By combining these previously known risk factors with CRF, more accurate SCD risk assessment can be made. This should be taken into account when considering treatment for patients with risk of SCD.

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**Obesity paradox in patients with acute heart failure: application of propensity score methodology in an acute heart failure database AHEAD**


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**Introduction:** Obesity has repeatedly been identified as an independent risk factor for the risk of death from heart failure. This may be given by several factors: presence of metabolic syndrome, increased diastolic blood pressure, or insulin resistance. In contrast to stated risk factors, recent studies reported obesity to be associated with a lower risk of death. However, obesity phenomenon is called “obesity paradox” (Curris M. Med Hypotheses 2008; 71: 130-4).

**Methods:** We conducted a retrospective analysis of patients who presented with heart failure (HF) and were eligible for study inclusion. Patients with acute coronary syndromes and those having other conditions leading to HF were excluded. The propensity score method decreased the in-hospital mortality in comparison to patients with normal weight.

**Conclusion:** The obesity paradox was confirmed, since the patients with obesity had lower in-hospital mortality in comparison to patients with normal weight.

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**Does admission pre-albumin predict in-hospital mortality in acute heart failure patients?**

P. Lourencz, S. Silva, F. Fries, M. Avelar, P. Torres Ramalho, T. Guimarães, P. Bettencourt, Sao Joao Hospital, Porto, Portugal

**Background:** Prognostic predictors of in-hospital mortality in acute heart failure (HF) have not been so fully studied as those for long term outcome in chronic HF. Malnutrition has been increasingly recognized as associated with poor outcome in HF. Pre-albumin as emerged as the best marker for protein malnutrition. We aimed to study if pre-albumin predicted in-hospital mortality in patients admitted with acute HF.

**Methods:** During a 20-month period, all patients admitted due to acute HF were included with an admission B-type natriuretic peptide (BNP) > 200 pg/ml were eligible for study inclusion. Patients with acute coronary syndromes and those having other conditions leading to HF were excluded. The propensity score method was used for selection of patients, who are comparable in their selected characteristics and parameters.

**Conclusion:** The obesity paradox was confirmed, since the patients with obesity had lower in-hospital mortality in comparison to patients with normal weight.
Thirty-two of the patients (4.8%) died in hospital. Patients dying in hospital were older, had lower admission systolic blood pressure, worse admission renal function and higher BNP. Patients with in-hospital death also had significantly lower total cholesterol: 12.5 (9.1-14.5) mmol/l vs 150 (126-186) in those discharged alive; lower albumin: 32.0 (4.0) vs 35.4 (4.8) mg/dl; and lower pre-albumin: 13.2 (5.2) vs 16.2 (7.1) mg/dl. Higher pre-albumin predicted in hospital survival with a HR of 0.89 (95% CI: 0.82-0.95, P < 0.001). Association with outcome was independent of other variables also associated with outcome in an univariate approach (systolic blood pressure, age, blood urea, BNP, total cholesterol and albumin). An admission pre-albumin < 18 g/l predicted in-hospital death with a HR of 5.64 (95% CI: 1.20-26.51, P < 0.03).

Conclusions: Malnutrition as assessed by lower pre-albumin predicted in-hospital death in patients admitted with acute HF. HF patients with admission pre-albumin < 18 g/l have more than five-fold higher risk of in-hospital death than those with higher admission pre-albumin.

Are total cholesterol levels important for hospital and long time prognosis of patients with acute heart failure?

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1Masaryk University, St. Anne’s Faculty Hospital, 1st Department of Internal Medicine, Cardioangiology, Brno, Czech Republic; 2Faculty Hospital, Masaryk University, Brno, Czech Republic; 3Charles University, Prague, Czech Republic; 4Faculty Hospital, Olomouc, Czech Republic; 5Hospital Na Homolce, Prague, Czech Republic

The purpose of this study was to evaluate if there is an association of total cholesterol levels with hospital and long time mortality of patients admitted for acute heart failure. The AHEAD MAIN Registry is a database conducted in 7 university hospitals, all with 24 hour cath lab service, in 4 cities in the Czech Republic. The database included 4 153 patients hospitalised for acute heart failure in the period 2006 – 2009. Median age was 73.8 years, 42% females, more than 70 years 60%, ejection fraction below 30% 37.9%. The data were collected prospectively using a database accessible via the Internet website and were evaluated continuously (including in-hospital mortality). The long-term mortality was followed in the centralised database of the Ministry of Health of the Czech Republic and recent data from the year 2010. The log rank test was used for the analysis of long term survival. The independent influence of total cholesterol level on mortality and survival was assessed using multivariate logistic regression and Cox proportional hazards model respectively. Of 4 153 patients, 526 (12.7%) patients died during hospitalisation. The median length of hospitalisation was 7.1 days (5.5 days for those patients who died and 9.7 days for those who were discharged home). 2 384 patients had complete records for total cholesterol levels – 946 females and 1 437 males were included in this analysis. The median total cholesterol level was 4.40 mmol/l. For the calculation of long term mortality, the cohort was divided into three groups: total cholesterol levels below 4.50 mmol/l, 4.50-5.49 mmol/l and above 5.50 mmol/l. Total cholesterol levels were important for hospital mortality for both genders (P < 0.001). In the long term follow up (78 months) patients with total cholesterol level below 4.5 mmol/l had the worst prognosis (P < 0.001). The independent influence of total cholesterol on hospital and long time mortality was confirmed in the multivariate analysis when total cholesterol level below 4.5 mmol/l was combined with other predictors revealed in the univariate analysis. Total cholesterol levels are important for in-hospital mortality and long term survival of patients admitted for acute heart failure.

The prognostic importance of evaluating nutritional status in patients with chronic heart failure


Yamagata University School of Medicine, Yamagata, Japan

Background: Low nutritional status is one of the unfavorable prognostic factors in some clinical setting. However, the association between nutritional indexes and outcomes in patients with chronic heart failure (CHF) is unclear. The purpose of this study was to clarify the impact of nutritional status on cardiac prognosis in patients with CHF.

Methods and Results: We evaluated controlling nutritional status score (CONUT), prognostic nutritional index (PIN), and geriatric nutritional risk index (GNIr) in consecutive 388 patients with CHF (mean 69.6±12.3 years) admitted to our hospital. CONUT consists of 2 biochemical parameters (serum albumin and total cholesterol level) and 1 immune indicator (total lymphocyte count). PIN consists of 1 biochemical parameter (serum albumin) and 1 immune indicator (total lymphocyte count). GNIr consists of 1 biochemical parameter (serum albumin) and ratio of body weight to ideal body weight. Patients were prospectively followed with the endpoints being cardiovascular death or rehospitalization. There were 130 events including 33 deaths and 97 rehospitalizations during a mean follow-up of 37.7 months. Patients with cardiac events showed higher age, more severe New York Heart Association (NYHA) functional class, lower prevalence of valvular heart disease, lower body mass index, lower serum triglyceride level, lower serum high-density lipoprotein cholesterol level and higher serum brain natriuretic peptide (BNP) compared with those without cardiac events. Further more, patients with cardiac events showed higher CONUT score (6.3±3.8 vs. 2.1±1.3, P<0.001), lower PIN score (151.2 vs. 26.4±3.7 vs. 38.6, 35.2±4.0, P<0.001), lower GNRI score (84.9, 76.8±92.3 vs. 95.3, 89.8±101.3, P<0.001) compared with those without cardiac events. In Cox proportional hazards analysis, CONUT (hazard ratio 40.9, 95% CI 8.4-154.8), PIN (hazard ratio 6.4, 95% CI 5.4-25.1), and GNRI (hazard ratio 11.6, 95% CI 3.7-31.0) were independently associated with cardiac events after adjustment of age, gender, NYHA functional class and serum levels of BNP. Among these nutritional indexes, CONUT had the highest hazard ratio. Kaplan-Meier analysis revealed a significantly higher cardiac event rate in patients with low nutritional indexes than in those without it.

Conclusion: Low nutritional status was associated with unfavorable outcomes in patients with CHF. It was suggested that evaluating nutritional status may provide a pivotal prognostic information in patients with CHF.

Heart failure: feast or famine? / Restenosis: still the achilles heel of percutaneous coronary interventions? 683

RESTITENOSIS: STILL THE ACHILLES HEEL OF PERCUTANEOUS CORONARY INTERVENTIONS?


Purpose: Stent fracture (SF) is associated with adverse events after drug-eluting stent implantation. However, few data exist on its long-term clinical impact in real world practice. Therefore, we evaluated the impact of SF on long-term clinical outcomes after sirolimus-eluting stent (SES) implantation.

Methods: Consecutive 2494 patients who had undergone the first SES implantation from November 2002 to December 2007 and received follow-up angiography within 12 months were analyzed. Angiographic stent fracture was defined as apparent separation of stent segments. Some tips, including focus image, inverse image, and image without catheter or contrast media were used to obtain the exact prevalence of SF. The incidence of clinical outcomes, including all-cause death, myocardial infarction (MI), stent thrombosis (ST), target lesion revascularization (TLR), and major adverse cardiac events (MACE, defined as all-cause death, MI, and TLR) was compared between SF and non-SF groups.

Results: Because 446 of the 2494 patients were excluded because of no angiographic follow-up within 12 months, the entire study population consisted of 2048 patients (3218 lesions) and was classified into two groups: 243 patients with SF and 1805 without SF. The median duration of follow-up was 4.9 years. At 4-year follow-up, the rates of TLR, MI, and MACE were significantly higher in the SF group than in the non-SF group (38.3% vs. 17.2%, p<0.001; 2.1% vs. 0.6%, p<0.03; 42.4% vs. 25.0%, p=0.001, respectively), whereas the rate of all-cause death was similar between groups (6.5% vs. 10.0%, p=0.20). The figure shows the cumulative incidence of definite or probable very late ST.

Figure 1. Cumulative incidence of very late stent thrombosis.

Conclusions: Our study suggests that SF is associated with higher rates of late adverse events except all-cause death after SES implantation.

Stent fracture and restenosis at stent fracture site after sirolimus-eluting stent and everolimus-eluting stent implantations: impact of stented vessel


Background: Stent fracture (SF) and its related restenosis are concerns of sirolimus-eluting stent (SES) implantation. However, everolimus-eluting stent (EES) may have a potential for the reduced prevalence of SF. We assessed SF and restenosis at SF site in terms of stented vessel after SES and EES implantations.

Methods: A total of 8817 stent-implanted lesions (SES 6000, EES 2217) from
November 2002 to March 2011 were analyzed at mid-term follow-up. Stented vessels were classified into two groups: right coronary artery (RCA) and non-RCA. Results: The table shows data. The SF rate of EES was significantly lower than that of SES in both RCA and non-RCA. The restenosis rate at SF site of EES was significantly lower in the non-RCA, but it was similar in the RCA.

Conclusion: Although EES reduced the prevalence of SF, the effect of EES on SF related restenosis depends on the vessel site.

4023
Decreased interleukin-33 serum levels after coronary stent implantation are protective against in-stent restenosis
S. Demyanets1, R. Jarai2, K. Katarsos3, S. Farhans1, A. Wornert1, W.S. Spedel1, J. Wotja1, K. Huber2. 1Medical University of Vienna, Vienna, Austria; 2Wilhelminen Hospital, Vienna, Austria
Background: Restenosis after stent deployment is an overreaction of the wound healing response after vascular injury and is characterized by the sequence of inflammation, granulation, and extracellular matrix remodeling. Interleukin-33 (IL-33) is a recently described member of the IL-1 family of cytokines and is a ligand for the ST2 receptor. Circulating IL-33 was increased in patients with inflammatory disorders such as rheumatoid arthritis, systemic sclerosis, inflammatory bowel disease and liver failure. However, the predictive value of IL-33 for the development of in-stent restenosis (ISR) is not known.
Methods: We included 387 consecutive patients undergoing percutaneous coronary intervention (PCI) of whom 193 had stable angina, 93 non-ST elevation myocardial infarction (NSTEMI), and 101 ST-elevation MI (STEMI), respectively. Blood was taken directly before and 24 hours after stent implantation. Plasma levels of IL-33 were measured by a specific ELISA. The presence of ISR was initially evaluated by clinical means. When presence of myocardial ischemia was suspected, coronary angiography was performed to confirm the suspected diagnosis of ISR.
Results: Bare metal stents (BMS) were used in 283 and drug eluting stents (DES) were used in 104 patients. Clinical ISR was present in total in 34 patients (8.8%). IL-33 was detectable in 185 patients and was below detection limit in 202 patients. In patients with decreased IL-33 (n=95), unchanged or non-detectable levels (n=210) or increased levels of IL-33 after PCI (n=82), ISR-rate was 2.1%, 9.5% and 14.6%, respectively (p<0.05). Accordingly, patients with ISR showed a significant increase of IL-33 upon PCI (p<0.05). This association was independent from clinical presentation and risk factors as well as numbers and type of stents.
Conclusion: In patients with both stable and unstable coronary artery disease, a decrease of IL-33 serum levels after stent implantation is associated with a lower rate of in-stent restenosis.

4024
Efficiency of statin treatment on EPC recruitment depends on baseline EPC titre, and does not improve angiographic outcome in coronary artery disease patients treated with the Genous stent
W. Den Dekker1, J.H. Hougraff1, S.M. Rowland2, S.P.M. De Boer1, R.J. De Winter1, P. Den Heijer1, F. Fijneman1, P.W. Serruyts1, C. Cheng1, H.J. Duckers1. 1Erasmus Medical Center, Thoraxcenter, Department of Cardiology, Rotterdam, Netherlands; 2Orthus Neich, Fort Lauderdale, United States of America; 3Academic Medical Center, Amsterdam, Netherlands; 4Amphia Hospital, Department of Cardiology, Breda, Netherlands
Objective: To assess the effect of high dose Atorvastatin treatment on endothelial progenitor cell (EPC) recruitment and angiographic and clinical outcome in coronary artery disease (CAD) patients treated with the GenousTM EPC capturing stent.
Methods: The HEALING IIB study was a multi-center, open-label, prospective trial that enrolled 100 patients. Patients were started on 80mg Atorvastatin qd, at least two weeks before index procedure and continued for at least four weeks after the index procedure.
Results: 87 Patients were included in this analysis. EPC levels significantly increased as early as 2 weeks after start of statin. Remarkably, among this group, 31 patients proved to be non-responder to Atorvastatin treatment (i.e. no increase in EPC levels) while 56 patients were responders (i.e. rise in EPC count between week -2 and 0). Compared to responders, non-responders had a significantly higher baseline EPC count (76±10 vs. 41±5, p<0.01) with a lower LLL at 6 and 18 month FU (0.61±0.07 vs. 0.88±0.06, 0.50±0.08 vs. 0.62±0.08 p<0.01 respectively, see figure). Furthermore, baseline EPC count inversely correlated with LLL at 6 month follow-up (FU) (R=0.42, p<0.001).
Conclusion: Patients with higher EPC count at baseline showed no increase in EPC recruitment in response to statin treatment but had favorable LLL at 6 and 18 month FU, whereas patients with lower EPC count were responsive to statin therapy but EPCs might be less functional as they had higher LLL at 6 and 18 month FU. These data imply that, although statin treatment can enhance EPC titre in these patients with low baseline levels, there is no indication for a possible beneficial clinical effect with EPC capture stents.

4025
Drug-eluting stents for the treatment of chronic total occlusion: a comparison with sirolimus, paclitaxel, zotarolimus, biolimusA9, EPC capture and everolimus-eluting stent: multicenter registry
S. Nakamura1, H. Ogawa1, J.H. Bae2, Y.H. Cahyadi3, W. Udayacharam1, D. Tresukosol1, S. Bansakawadi1, 1New Tokyo Hospital, Chiba, Japan; 2Kumamoto University Hospital, Kumamoto, Japan; 3Konyang University Hospital, Daejeon, Korea, Republic of; 4Husada Hospital, Jakarta, Indonesia; 5King Chulalongkorn Memorial Hospital, Bangkok, Thailand; 6Faculty of Medicine Siriraj Hospital of Mahidol University, Bangkok, Thailand
Aim: The aim of this study is to compare the safety and efficacy of Sirolimus (SES), Paclitaxel (PES), Zotarolimus (ZES-R; Endeavor Resolute), BiolimusA9 (BES), EPC capture (ECS) and Everolimus-eluting stent (EES) on the outcome of patients with chronic total occlusion (CTO).
Methods: A prospective analysis of 1576 patients with 1738 CTOs (396 SES, 526 PES, 219 ZES-R, 209 BES, 148 ECS, 240 EES) in six high volume Asian centers after successful recanalization of CTO was performed. The study endpoints were 30 days and 12 months major adverse cardiac events (MACE), 12 months angiographic restenosis and target lesion revascularization (TLR).
Results: See table for clinical results.

### Differences in progression pattern of late restenosis after drug-eluting stent implantation

Background: Recently, late restenosis after drug-eluting stent (DES) has been reported. However, the impact of DES type on the prevalence and progression pattern of late restenosis remains unclear. Thus, we evaluated the prevalence and progression pattern of late restenosis after sirolimus-eluting stent (SES), paclitaxel-eluting stent (PES), zotarolimus-eluting stent (ZES), and everolimus-eluting stent (EES) implantation.
Methods: From November 2002 to May 2010, 6811 consecutive patients (8879 lesions) were treated with SES, PES, ZES, and EES (SES, 6291 lesions; PES, 1519; ZES, 561; EES, 508) and performed midterm follow-up coronary angiography.

### Table 1. SF rate and restenosis rate at SF site

<table>
<thead>
<tr>
<th>DES Type</th>
<th>SF Rate (%)</th>
<th>Restenosis Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SES</td>
<td>7.1</td>
<td>7.5</td>
</tr>
<tr>
<td>PES</td>
<td>9.4</td>
<td>6.4</td>
</tr>
<tr>
<td>ZES-R</td>
<td>7.0</td>
<td>6.4</td>
</tr>
<tr>
<td>BES</td>
<td>6.4</td>
<td>5.9</td>
</tr>
<tr>
<td>ECS</td>
<td>4.5</td>
<td>4.5</td>
</tr>
</tbody>
</table>

### Conclusion

The use of drug-eluting stents in patients with CTO was safe with low acute complication. Patients treated with 2nd generation DES such as ZES-R, BES and EES showed lesser rate of restenosis compared with 1st generation drug-eluting stents.

### Table 2. Clinical Results

<table>
<thead>
<tr>
<th>Procedure</th>
<th>SES</th>
<th>PES</th>
<th>ZES-R</th>
<th>BES</th>
<th>ECS</th>
<th>EES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural success (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>MACE at 30 days (%)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>MLD at baseline (mm)</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
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<tr>
<td>12 months MLD (mm)</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Restenosis rate (%)</td>
<td>7.1</td>
<td>7.1</td>
<td>7.1</td>
<td>7.1</td>
<td>7.1</td>
<td>7.1</td>
</tr>
</tbody>
</table>

### Figures

**Figure 1. SF rate and restenosis rate at SF site**
Regional differences in the use of antithrombotic therapy for stroke prevention in atrial fibrillation: European and Asian insights from the Global Anticoagulant Registry in the FIELD (GARFIELD)


Methods: We analysed the dataset of the AMADEUS trial, which was a multicentre, randomised, non-inferiority study that compared fixed-dose idraparinux with adjusted-dose oral vitamin K antagonist (VKA) therapy in patients with AF. The principal safety outcome was “any clinically relevant bleeding” that was a composite of “major bleeding” and “clinically relevant non-major bleeding”.

Results: The AMADEUS study randomized 2293 patients in the VKA arm (65% men, mean age 70.2 ± 9.1). In total 251 (11%) clinically relevant bleedings occurred including 39 (1.7%) major bleedings. The HAS-BLED score performed best in predicting “any clinically relevant bleeding” as reflected both by the AUC (Table 1) and net reclassification improvement (NRI HAS-BLED = 0.14, p = 0.0004 and NRI HAS-BLED vs. ATRIA = p = 0.004). In the ROC analysis the ATRIA score failed to demonstrate any predictive value for the above endpoint. All bleeding risk stratification schemas perform equally well in predicting major bleeding.

Conclusions: The HAS-BLED score performed significantly better in predicting “any clinically relevant bleeding”. Given its simplicity and superior performance to other scores, the HAS-BLED score would be more attractive for the estimation of OAC-related bleeding risk in clinical practice.

Table 1. Comparison of areas under the curve (AUC, or c-statistic) and Net Reclassification Improvement (NRI) for HEMORR2HAGES, ATRIA and HAS-BLED

<table>
<thead>
<tr>
<th>Analysis</th>
<th>AUC</th>
<th>95% CI</th>
<th>p</th>
<th>AUC</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAS-BLED vs. ATRIA</td>
<td>0.61</td>
<td>0.51-0.7</td>
<td>0.013</td>
<td>0.55</td>
<td>0.47-0.62</td>
<td>0.013</td>
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<tr>
<td>HAS-BLED vs. HEMORR2HAGES</td>
<td>0.62</td>
<td>0.52-0.71</td>
<td>0.012</td>
<td>0.56</td>
<td>0.51-0.61</td>
<td>0.012</td>
</tr>
<tr>
<td>ATRIA vs. HEMORR2HAGES</td>
<td>0.65</td>
<td>0.56-0.73</td>
<td>0.002</td>
<td>0.60</td>
<td>0.50-0.70</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Regions were defined as: 1-3 European countries, 4-5 European countries, 6-7 Asian countries, 8-10 respectively.

Background: The estimation of the risk of serious bleeding is a crucial step in the management of atrial fibrillation (AF) patients taking anticoagulants.

Three bleeding risk prediction schemes have been validated in AF populations: HEMORR2HAGES, ATRIA and HAS-BLED.

Methods: We analyzed the dataset of the AMADEUS trial, which was a multicentre, randomised, non-inferiority study that compared fixed-dose idraparinux with adjusted-dose oral vitamin K antagonist (VKA) therapy in patients with AF. The principal safety outcome was “any clinically relevant bleeding” that was a composite of “major bleeding” and “clinically relevant non-major bleeding”.

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<th>p</th>
<th>AUC</th>
<th>95% CI</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>HAS-BLED vs. ATRIA</td>
<td>0.61</td>
<td>0.51-0.7</td>
<td>0.022</td>
<td>0.55</td>
<td>0.47-0.62</td>
<td>0.022</td>
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<tr>
<td>HAS-BLED vs. HEMORR2HAGES</td>
<td>0.62</td>
<td>0.52-0.71</td>
<td>0.002</td>
<td>0.56</td>
<td>0.51-0.61</td>
<td>0.002</td>
</tr>
<tr>
<td>ATRIA vs. HEMORR2HAGES</td>
<td>0.65</td>
<td>0.56-0.73</td>
<td>0.001</td>
<td>0.60</td>
<td>0.50-0.70</td>
<td>0.001</td>
</tr>
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Regions were defined as: 1-3 European countries, 4-5 European countries, 6-7 Asian countries, 8-10 respectively.
and 5 strokes (0.99%/year) and 10 major bleeding events (1.97%/year) in the warfarin group (continuing on VKA), in the 30 days after stopping study drug with the majority of the imbalance after the first week (Table). This pattern mirrored the first 30 days of warfarin where warfarin-naive patients starting warfarin had a higher rate of stroke or systemic embolism (5.41%/year) than warfarin-experienced patients (1.41%/year). No similar increase in event rate was seen in the apixaban group following study drug discontinuation before the end of the trial.

**Conclusions:** The excess in thrombotic and bleeding events in the apixaban arm after study drug discontinuation at the end of ARISTOTLE seems to be related to an increased risk associated with the new initiation of a VKA that extends over several weeks rather than a direct effect of apixaban.

**4047 Stroke prevention in non-valvular atrial fibrillation: long-term results after 6 years of the watchman left atrial appendage occlusion pilot study**

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**Background:** Patients with non-valvular atrial fibrillation (NVAF) are at enhanced risk of embolic stroke; it has been reported more than 90% of left atrial thrombi in NVAF patients are found in the left atrial appendage (LAA).

**Methods:** The Watchman LAA Closure device (Boston Scientific, Plymouth, MN) is made of nitinol, incorporates fixation barbs around its perimeter and has a porous membrane on its atrial surface. A multi-center pilot study was initiated in August 2002. Patients were assessed at 45 days, 6 months and one year with transesophageal echo (TEE) and clinically assessed annually.

**Results:** Of 75 patients enrolled, the device was implanted successfully in 66. Anatomic limitations prevented implantation in 7, failure of venous access and an earlier generation delivery cable problem resulted in the other 2 unsuccessful procedures. Mean follow up was 73±25 months for all patients and 92±8 months for patients who were still actively followed. Mean age was 68±5 years at enrollment. The acute procedural success had been published previously. After 6 months, 92% had discontinued warfarin therapy and at the present time, 91% remain off warfarin therapy. On routine 6 month TEE follow-up, 4 patients were noted to have a thrombus layer along the atrial face of the implant, one of whom developed a transient ischemic attack (TIA). Warfarin was restarted in these 3 patients for 3 months without further evidence of thrombus. Two patients had an embolic stroke; one at 2 months and one at 39 months in the setting of severe concurrent cardiac disease. These data reflect an actual stroke rate of 0.5% (2 events in 402 patient years); the expected stroke rate given a mean CHA2DS2-VASc Score of 1.8±1.1 would have been 5.75%. Fifteen patients have died (mean 49±21 months), all deaths were non-device and non-procedure related.

**Conclusions:** The long-term data suggest that WATCHMAN LAA Closure is safe and feasible, with two embolic strokes through 6 years of active follow up. This reflects a 90% lower stroke rate as compared with the expected stroke rate according to the CHA2DS2-score.

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**4046 CHA2DS2-VASc score and thromboembolic and bleeding complications after successful cardioversion of acute atrial fibrillation**

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**Purpose:** It has been common practice to perform cardioversion of acute (≤48 hours) atrial fibrillation without anticoagulation. The objective was to determine the incidence of thromboembolic and bleeding complications related to cardioversion of acute atrial fibrillation in patients with and without perioperative anticoagulation.

**Subjects and methods:** A total of 5652 cardioversions were performed in 2569 consecutive patients with atrial fibrillation lasting ≤48 hours in three hospitals. For this analysis, embolic and bleeding complications were evaluated in 1632 cardioversions and 4420 cardioversions with no perioperative anticoagulation.

**Results:** Cardioversions were successful in 5362 (94%) cases. Thirty-eight thromboembolic events (35 patients) occurred within 30 days after cardioversions. All were after successful procedures and 29 (76.3%) were strokes. One patient had simultaneous stroke and peripheral embolisation after one cardioversion. All were after successful procedures and 29 (76.3%) were strokes. One patient had simultaneous stroke and peripheral embolisation after one cardioversion.

**Conclusions:** The incidence of postcardioversion thromboembolic complications is high in patients with high CHA2DS2-VASc score after cardioversion of acute atrial fibrillation when no anticoagulation is used. The present data supports the view that effective anticoagulation should be used in these patients also during cardioversions of short attacks of atrial fibrillation.

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**4048 Apixaban and warfarin are associated with a low risk of stroke following cardioversion for atrial fibrillation: results from the ARISTOTLE Trial**

G. Flaker1, R. Lopez2, S. Al-Khail3, A. Hermoso4, L. Thomas2, J. Zhu5, W. Ruizolo5, P. Mohan6, C. Grainger7, L. Wallentin8 on behalf of Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, apixaban 5 mg bid reduced stroke, death, and caused less bleeding as compared to warfarin (INR 2.0-3.0) in patients with atrial fibrillation and risk factors for stroke. During the trial if cardioversion was performed, it was recommended that investigators continue randomised treatment before and after the procedure. Thromboembolic events including stroke, systemic embolism, and myocardial infarction were compared between patients receiving apixaban or warfarin.

**Results:** Of 19,201 patients were included in the ARISTOTLE trial. A total of 577 (3.2%) patients underwent cardioversion during the trial including 286 (49.6%) assigned to apixaban and 291 (50.4%) assigned to warfarin. The median time to cardioversion was 5 months and approximately 75% of the procedures occurred by follow-up year one. Key baseline characteristics including gender, CHA2DS2 score, LVEF, and estimated duration of AF were similar in patients receiving apixaban and warfarin. In the first 90 days, no patient in either group suffered a stroke or systemic embolism. After cardioversion for a median follow-up of 233 days (range 1-489) in the apixaban group and 393 days (range 213-607) in the warfarin group, the composite of stroke, systemic embolism, and myocardial infarction occurred in 5 patients assigned to apixaban and 6 patients assigned to warfarin.

**Conclusions:** In patients with atrial fibrillation and risk factors, the risk of thromboembolic events after cardioversion is low in patients treated with either apixaban or warfarin. Apixaban appears to be a safe alternative to warfarin for stroke prevention after cardioversion.

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**CORONARY ARTERY DISEASE: FROM THE DARK TO THE LIGHT OF MULTIDETECTOR COMPUTED TOMOGRAPHY**

**4044 Stroke prevention in non-valvular atrial fibrillation: long-term results after 6 years of the watchman left atrial appendage occlusion pilot study**

K. Osuka1, S. Fukuda2, A. Tanaka3, K. Nakashima4, M. Sakaamoto5, J. Tabuchi6, J. Yonokawa7, K. Shimizu8, M. Yoshikawa9,1 on behalf of the Japan Watchman Clinical Study Group

**Purpose:** Recent studies have reported a close relationship between ring-like sign on coronary computed tomographic angiography (CCTA) and thin-cap fibroatheroma (TCFA). The aim of this study was to determine the predictive value of ring-like sign on CCTA for future acute coronary syndrome (ACS) events in patients with coronary artery disease (CAD).

**Methods:** This study consists of 895 consecutive patients who underwent CCTA examination and followed for more than 1 year. The primary end-point was ACS events (cardiac death, non-fatal myocardial infarction, and unstable angina pectoris). The CCTA analysis included the presence of positive remodeling (PR: remodeling index > 1.1), low-attenuation plaque (LAP: plaque with <30 Hounsfield units), and ring-like sign.

**Results:** Of 12,727 segments in 895 patients, 1,174 contained plaque, including plaques with PR in 130 (1.0%) segments, LAP in 107 (0.8%) segments, and ring-like signs in 45 (0.4%) segments. During the follow-up period (2.3±1.8 years),...
24 (2.6%) patients suffered ACS events. Of the 45 plaques with ring-like sign, 6 (13%) resulted in ACS in the first 1 year, and an additional 2 (4.4%) resulted in ACS in 1 to 2 years (Figure A). Cox proportional hazards models analysis showed that PR (p=0.05), LAP (p=0.05) and ring-like sign (p<0.05) were independent predictive factors for future ACS events. Plaques with ring-like sign showed higher risk for ACS events compared to those without ring-like sign (hazard ratio: 22.7; 95% confidence interval: 3.457; p<0.001). ACS events arose more frequently from PR, LAP, ring-like signs, and combinations thereof than with any other features (Figure B).

Conclusions: The present study demonstrated that the detection of ring-like sign on CCTA could help us to identify patients at high risk for future ACS events.

Prevalence of coronary artery anomalies in 8,002 consecutive patients: study with coronary computed tomography angiography

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Purpose: Anomalous coronary arteries originating from the opposite sinus of Valsalva (ACAOS) have been related to sudden cardiac death and account for 0.1% of cases reported by coronary angiography. We aimed to investigate the incidence of ACAOS in a population referred for coronary computed tomography angiography (CTA) at a single high-volume center.

Methods: A total of 8,002 consecutive patients were evaluated with dual-source CCTA between February 2008 and January 2012. The origin and course of ACAOS were analyzed in axial, multiview and volume rendering reconstructions. On the basis of CTA findings, the proximal course of each vessel was classified into the following subtypes: 1. anterior; 2. interarterial; 3. septal; and 4. retroaortic. In addition, 4 malignant features of the proximal portion of ACAOS were recorded as follows: a slitlike ostium, an acute angle of take-off from the coronary artery.

Results: Of the 45 plaques with ring-like sign on CTA, the aorta, an intramural course within the aortic wall, and a lateral indentation of the pulmonary trunk.

Conclusions: A total of 59 patients (29 male, 23-85 years) with ACAOS were identified. The incidence of ACAOS was 0.74%, (58/8002). The origins and course of ACAOS were clearly visualized in all patients, including right-sided origin of the left main or the left anterior descending coronary artery (n=16), right-sided origin of the left main coronary artery (n=10), retroaortic origin of the right coronary artery (n=16). Among analyzed subtypes of ACAOS, 19 (0.24%) had an interarterial course of which 11 (0.14%) showed a significant compression between the aortic root and the pulmonary trunk. The presence of both ACAOS and ACAOS was identified in 5 (0.06%) right coronary arteries arising from the left sinus of Valsalva.

The Prevalence of ACAOS Courses

<table>
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<tr>
<th>Course</th>
<th>RCA arising from the left sinus of Valsalva (n=16)</th>
<th>LM or LAD arising from the right sinus of Valsalva (n=16)</th>
<th>LAD or LCA arising from the left sinus of Valsalva (n=10)</th>
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<tbody>
<tr>
<td>RCA</td>
<td>16</td>
<td>12</td>
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<tr>
<td>LM</td>
<td>1</td>
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<td>LAD</td>
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Conclusion: Dual-source CCTA allows accurate and noninvasive identification of ACAOS, which are found more frequently compared to previous angiographic studies. The malignant characteristics of the proximal ACAOS might be exclusively associated with left-sided origin of the right coronary artery.

Prognostic significance of pre-test probability of coronary artery disease to coronary CT angiography in patients with coronary calcium score zero

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Background: Both coronary artery calcium score (CACS) and pre-test probability of risk stratification are considered as a gatekeeper to coronary computed tomography angiography (CTA). However, there was no report about the impact of different pre-test probabilities of CACD on the prognostic value of CACS zero for future cardiac events. The aim of this study was to evaluate the prognostic impact of pre-test probability prior to coronary CTA in patients with CACS zero.

Methods: The study group consisted of 297 patients (61.2±10.8 years) with CACS zero. The pre-test probability was determined using the modification of Diamond and Forrester method based on age, gender, and symptoms. Cardiac events
were deemed as cardiac death, nonfatal myocardial infarction, unstable angina requiring hospitalization, or coronary revascularization. Cardiac event-free survival was estimated using the Kaplan-Meier survival methods with log-rank statistics. The associations of selected variables with outcome were assessed in the multivariate Cox proportional hazard models.

Results: A very low, low, intermediate or high pre-test probabilities was observed in respectively 11% (90 patients), 41% (414 patients) and 5% (87 patients) of study patients. During follow-up (736±337 days), a total of 12 (4.0%) cardiac events occurred including nonfatal myocardial infarction in 1 (0.3%), unstable angina requiring hospitalization in 2 (0.6%) and coronary revascularization in 9 (0.3%). In this study of 12 patients with cardiac events, 5 patients (41.7%) with a high pre-test probability of CAD, 3 (25%) with an intermediate, and 4 (33.3%) with a low were observed. Kaplan-Meier event-free survival rate in patients with very low, low, intermediate and high risk pre-test probability of CAD was 0%, 3.3%, 2.4% and 29.4%, respectively. Patients with high pre-test probability had significantly more cardiac events as compared with very low, low and intermediate pre-test probabilities (p < 0.001). The event rate was 0% among patients with very low pre-test probability. Multivariate model revealed that high pre-test probability was the only significant predictor of cardiac events (risk ratio 11.3, 95% confidence interval 3.5-36.8).

Conclusion: CAGS zero by MDCT did not predict future cardiac events completely. The prognostic value of pre-test probability of CAD for patients with very low risk, low, and intermediate was excellent. The cardiac event rate was 0% among patients with very low pre-test probability. Coronary CTA could be avoided for these patients, especially those with very low pre-test probability.

Impact of lipid lowering on prevention of plaque progression detected by coronary computed tomography angiography.


Purpose: There are some reports that the severity of coronary artery stenosis by coronary computed tomography angiography (CTA) was associated with cardiac event rate. So, it would be important to find out the optimal treatment for prevention of plaque progression. Our previous study showed that serial CTA was useful to evaluate the plaque volume change of coronary arteries noninvasively. The aim of this study was to investigate the factors associated with the plaque progression of coronary arteries detected by CTA.

Methods: We studied 199 patients (84% male, mean age 66±10 years) undergoing CTA twice for any purpose. The median period from 1st to 2nd CTA was 9 months. Coronary artery plaques were compared between 1st and 2nd CTA, and patients were classified into two groups; progression group (n=27) and non-progression group (n=172). The patients background and laboratory findings contributed to plaque progression were investigated.

Results: Coronary risk factors were similar in two groups. There were no significant differences in high density lipoprotein cholesterol, low density lipoprotein cholesterol (LDL-C), triglyceride, glucose level, and Hemoglobin A1c between two groups at baseline. In progression group, total cholesterol at baseline (209±39 vs 193±37 mg/dl p=0.0359) was significantly higher, however, there was no significant different at 2nd CTA. Patients on statin was not significant different both at 1st (44.4 vs 45.4%, p=0.9001) and 2nd CTA (59.3±76.6%, p=0.0745) between progression and non-progression group. At 2nd CTA, LDL-C (110±34 vs 96±31 mg/dl p=0.0274) was significantly higher in progression group than non-progression group. Furthermore, patients with LDL-C >100mg/dl at 2nd CTA were significantly more frequent in progression group (74.1 vs 37.6%, p=0.0004). Cut-off value regression progression by CTA was determined at 130 mg/dl Receiver Operating Characteristic curve, and sensitivity and specificity were 74.1% and 61.4%, respectively.

Conclusions: Plaque progression of coronary arteries by CTA was associated with poor control of LDL-C level at 2nd CTA. The present study confirmed that LDL-C <100mg/dl was reasonable for secondary prevention of coronary artery disease. CTA might have potential to provide the optimal strategies for improvement of prognosis.

POSTER SESSION 5
GENETIC ASPECTS/VENTRICULAR ARRHYTHMIAS

Outcome of screening of relatives to patients with long QT syndrome: a nationwide Danish study.

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Aims: According to international recommendations relatives to patients with long QT syndrome (LQTS) are offered cascade screening. In this Danish study we assessed the outcome of clinical and genetic cascade screening of LQTS families nationwide.

Methods and results: Patients with LQTS were identified from Danish national registers and patient files were reviewed. A total of 286 patients with LQTS were identified in 79 families and included 209 relatives. The majority of diagnosed relatives identified by cascade screening were asymptomatic. Symptomatic probands and family members most often presented with syncope, followed by aborted cardiac arrest (abSCD), unspecific symptoms and sudden cardiac death (SCD). Syncope, abSCD and SCD most often occurred at rest. The most pronounced QTc prolongation was seen in probands and patients with serious cardiac events. A disease-causing mutation was found in 59 probands (81% of 73 probands tested). The majority of mutations were localized to the KCNHzh1 gene (63%). A total of 180 (63%) patients were on beta-adrenergic blocking agents (BB) and 67 (23%) patients had an implantable cardiac defibrillator (ICD). Appropriate ICD therapy was given to 12 (29%) probands and three (12%) family members. Fourteen (33%) probands and two (8%) family members experienced ICD complications.

Conclusions: By cascade screening we identified almost 3 affected relatives for each proband. Probands were noteworthy more clinically affected compared to the relatives, but a considerable fraction of the diagnosed relatives were symptomatic and 14 family members (7%) fulfilled guideline criteria for ICD implantation.

A new MOG1 transcript variant implicated in arrhythmias.

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A missense mutation in the Mog1 gene has been recently identified in one Brugada syndrome (BrS) patient. This gene has been shown to interact with the cytoplasmic loop II (between transmembrane domains DII and DIII) of Nav 1.5. This interaction plays a critical role in the regulation of sodium current density, increasing the whole-cell INa current. In our study we screened a cohort of 161 BrS and 79 IVF (idiopathic ventricular fibrillation) patients by direct sequencing on all the three alternative transcript variants of the Mog 1 gene. All patients were screened positive for mutations on the SCN5A, CACNA1c and GPID1L, associated with BrS.
A novel mutation affecting the transmembrane domain of the KCNJ2 protein is associated with high prevalence of life-threatening ventricular arrhythmias in a family with Andersen-Tawil syndrome

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Abstract: Andersen-Tawil syndrome is a rare inherited multisystem disorder associated with mutations in KCNJ2 and relatively low prevalence of ventricular arrhythmias. Our aim was to describe the clinical course of ATS in a family, in which the proband survived aborted cardiac arrest (ACA) and genetic screening revealed a previously unknown mutation (c.271_282del12p.Ala91_Leu48del), resulting in the loss of four amino acids in the first transmembrane domain of the KCNJ2 protein.

Methods: A cascade family screening was performed in a 5-generation family upon identification of the KCNJ2 mutation in the proband. Subsequently, 10 of 21 screened individuals appeared to be mutation carriers (median age 38 range [10-75] years, 3 female). Mutation carriers underwent clinical examination including biochemistry panel, cardiac ultrasound, Holter ECG and exercise stress test. Genotype-positive family members were followed-up for a median of 36 months (range 26-48 months).

Results: 1) At baseline, 2 patients survived ACA, 3 had syncope or presyncope attacks and 2 reported palpitations. Exercise-induced nonsustained bidirectional ventricular tachycardia was documented in 4 patients, 2 of whom received implantable cardioverter-defibrillators (ICD) for primary prevention and 2 for secondary prevention. 2) During follow-up, 1 primary prevention and 1 secondary prevention patient received in total 4 adequate ICD shocks. In total, life-threatening ventricular arrhythmias included 2 episodes of ventricular fibrillation with shock and cardiac arrest, 2 episodes of ventricular tachycardia with shock, 3 episodes of ventricular tachycardia with or without shock, 1 episode of atrial fibrillation with or without shock, and 2 episodes of nonsustained ventricular tachycardia. All patients underwent implantation of an ICD with a programmer and were treated with the muscarinic agonist, carbachol. 3) Mutation carriers predestined continued to experience minor ventricular arrhythmias and sudden death. Only 1 patient suffered from periodic paralysis, and 1 had renal dysplasia requiring extirpation at the age of 3. All patients were on normal serum potassium level and repeated assessments remained normal and none had any othercardiac diagnosis manifested.

Conclusion: Our findings suggest that the novel KCNJ2 mutation is associated with a predominantly cardiac phenotype of Andersen-Tawil syndrome with high propensity to life-threatening ventricular arrhythmias.

Inherited cardiovascular diseases (ICVDs) in the every day clinical practice: diagnostic yield and genetic family screening

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1 Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens; 2Thriassio Hospital, Medical Center of Naxos, Naxos, Greece

Purpose: ICVDs have variable clinical expression and incomplete penetrance. The aim of this study is to identify the diagnostic yield of genetic testing on each disease in every day clinical practice and the response of family members to family screening.

Methods: 109 probands were clinically diagnosed with Hypertrophic Cardiomyopathy (HCM), Long QT syndrome (LQTS), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), Dilated Cardiomyopathy (DCM-LMNA), Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), Brugada syndrome (BrS) and Marfan syndrome (MFS) according to the latest diagnostic criteria for each disease and molecular genetic analysis was performed. Family members (n=210 out of 352 that were invited) of mutation positive probands (n=58) were clinically and genetically evaluated. Available data were used to evaluate the impact of sudden death (SD) on the number of relatives that accepted to be tested.

Results: A pathogenic mutation was identified in 58 out of 109 (52.9%) index cases suffering from the above mentioned ICVDs. In most common ICVDs (HCM, LQTS, ARVC, BrS), the Mut(+)-Phen(-) relatives reached an average of 30.2% (Table). We categorized the families on SD-families and non-SD-families regarding the presence or not of SD on their pedigrees. On SD-families, we suggested on 198 relatives to be tested while 130 of them proceeded on genetic screening. Similarly, 80 out of 154 relatives were tested on non-SD-families. Relatives response on genetic screening is strongly stimulated by the presence of a SD case in the family (OR: 1.91; CI: 1.24-2.96, p: 0.003).

Conclusion: The diagnostic yield coming from ICVD clinic is satisfactory in most of the cases. The experience of a SD in a family motivates relatives to accept better the usefulness and the economic burden of genetic family screening. The importance of genetic testing as a prophylactic health approach should be further highlighted.

Long QT3 mice have disrupted sympathovagal balance and in vivo ventricular stimulation does not determine risk of sudden cardiac death, suggesting that a second perturbation may be required

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Purpose: Long QT 3 (LQT 3) is a cause of sudden cardiac death (SCD) by Tor- sades de pointes (TdP). SCD often occurs during sleep, rest and bradycardia, suggesting that heightened parasympathetic tone provokes TdP in LQT 3. It is challenging to ascertain the risk of SCD in these patients. We performed in vivo electrophysiological studies (EPS), ventricular tachycardia (VT) stimulation and telemetry in LQT 3 (XKPO) and wild type (WT) mice, without and with provocation with the muscarinic agonist, carbachol.

Methods: EPS were performed in young (8-week) and old (≥6 months of age) anaesthetised mice with a 1.1 F catheter inserted into the right ventricle via the
The effect of corticosteroid, antiarrhythmic agents, and radiofrequency catheter ablation on ventricular tachycardia associated with cardiac sarcoidosis

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Purpose: Ventricular tachycardia (VT) and sudden death are commonly observed in cardiac sarcoidosis, however, the clinical impact of a multimodality therapy is still uncertain.

Methods: We enrolled 35 patients (55±12 years, 11 male) who had a diagnosis of sustained VT associated with cardiac sarcoidosis. All patients were initially treated with corticosteroids and antilaarrhythmic agents unless they refused to take them. Steroid therapies were started with an initial dose of 30 mg/day, and the dose was gradually increased over a period of 6 to 12 months to 5±10 mg/day as a maintenance dose. If the VTs recurred even on the antiarrhythmic and steroid therapy, radiofrequency catheter ablation (RF-CA) was performed. Patients who underwent RF-CA before being medicated, including with corticosteroids and antiarrhythmic agents, were excluded from this study. The clinical impact of both a steroid and antiarrhythmic therapy associated with RF-CA was evaluated.

Results: All patients received antiarrhythmic drugs and 32 patients received steroid therapy. During a 51±37 month follow-up, 22 (66%) patients were free from any VT episodes. The ejection fraction and prevalence of a Galilum-67 uptake was lower in those with VT recurrence than in those without (40.1±12% vs. 54±6%, p<0.05; 22% vs. 91%, p<0.001, respectively). The multivariate Cox regression analysis demonstrated that the absence of a Galilum-67 uptake in the heart was an independent predictor for a VT recurrence under the drug therapy ( Hazard ratio 9.5, 95% confidence interval 1.1 to 80.4; p<0.01). The 10 patients who experienced VT recurrence underwent RF-CA. An electrophysiologic study revealed that the mechanism of VT could be classified into 2 subgroups that were Purkinje related VT and scar related VT. The VT-QRS duration was narrower in Purkinje related VT than in scar related VT (149±13 ms vs. 181±26 ms; p<0.01). After a mean follow up of 24±11 months, 6 of 13 patients experienced VT recurrences. The number of induced and sustained VTs was higher in the patients with VT recurrences than in those without (9.2±2.5 vs. 2.7±1.8; p<0.05, 40.3±14 vs. 2.0±8; p<0.01, respectively). An ROC curve revealed that the number of induced VTs of more than 4 identified VT recurrences after RF-CA for VT recurrence was statistically higher in 63% and specificity of 86%.

Conclusions: The multimodality therapy for VT associated with cardiac sarcoidosis could successfully suppress VT recurrences in 63% of the patients.

Changes in NT-proBNP level after successful PVC ablation in patients without structural heart disease: evidence for PVC-induced chronic wall stress

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Purpose: NT-proBNP is synthesized in ventricular myocardium in response to increased wall stress. A high, chronic PVC burden has been associated with a reversible cardiomyopathy. However, the majority of patients with symptomatic PVCs presents with only slightly impaired or normal LV function. We evaluated NT-proBNP levels before and after ablation to determine the potential wall stress caused by PVCs in symptomatic patients with slightly impaired or normal LV function.

Methods: Eighty patients (42 male, 48±16 y) with a LVEF>50%, referred for ablation due to 11% of PVCs, were included in this study. NT-proBNP levels were measured before and 3 months after ablation. NT-proBNP levels were defined as PVC burden reduced of ≥80% on Holter monitoring. Patients were divided into 2 groups according to LVEF prior to ablation: Group 1, slightly impaired LVEF (50-60%); Group 2, normal LVEF (>60%).

Results: Group 1 consisted of 33 patients (41% and Group 2 of 47 patients (59%). Age (47±17 vs. 48±185 y, p<ns), symptom duration (49±64 vs. 44±47 months, p=ns), PVC burden (28±14 vs 23±13%, p<ns) and baseline NT-proBNP levels (98ng/L [QR 60-384] vs 124ng/L [QR 59-149ng/L]; p<ns) did not differ between groups. Ablation was successful in 28 patients in Group 1 (85%) and 41 patients in Group 2 (87%). All patients with PVC burden reduction ≥80% were asymptomatic after ablation, NT-proBNP levels decreased significantly during follow-up (to 61ng/L [QR 28-120ng/L], p<0.001 in Group 1 and to 52ng/L [QR 31-76ng/L], p<0.001 in Group 2). In contrast, NT-proBNP levels did not decrease in patients with a PVC burden reduction of <80% in either group.

Conclusion: NT-proBNP levels decreased significantly after successful PVC ablation suggesting that frequent PVCs cause chronic increased wall stress even in the absence of marked LV dysfunction. Increased wall stress may explain symptoms of fatigue and exercise intolerance despite a slightly impaired or normal LV function, and development of a cardiomyopathy in the long term in some patients.
P4094 The characteristics of malignant premature extrasystoles originating from right ventricular outflow tract

Premature extrasystoles (PES) originating from right ventricular outflow tract (RVOT) are often observed in patients without structural heart diseases and are generally considered as benign ventricular arrhythmias. However, ventricular fibrillation (VF), and/or polymorphic ventricular tachycardia (PVT) are occasionally initiated by the PES. The aim of this study was to clarify how to differentiate malignant (M) PES from benign (B).

Methods: Consecutive 30 patients, in whom radiofrequency catheter ablation was conducted for PES originating from RVOT, were enrolled. Spontaneous VF and/or PVT initiated by the PES were showed in 9 patients (M-gr). Coupling interval, QRS duration, QRS morphology and optimal ablation site of the PES in M-gr were compared with them in the other 21 patients group (B-gr).

Results: There were no differences between M-gr and B-gr in coupling interval (419 ± 90 vs. 438 ± 111 msec, ns) and QRS duration (166 ±1 ± 111 vs. 153 ±15 msec, ns). The prevalence of notch on QRS in inferior leads of PES was significantly higher in M-gr than in B-gr (9/9 vs. 3/21, p < 0.01). Broad R wave (>120msec) in I was significantly more frequently observed in M-gr than in B-gr (7/9 vs. 1/21, p < 0.01). The prevalence of aVF/aVL (the ratio of negative amplitude of aVF to aVL) > 1 was not significantly higher in M-gr than in B-gr (7/9 vs. 4/21, p > 0.05). M-gr patients had free wall in 7 out of 9 patients in M-gr, and 1 out of 21 patients in B-gr (p < 0.01).

Conclusion: In conclusion, PES originating from posterior side of free wall in RVOT, with notch in inferior leads and/or broad R wave in I, frequently initiate VF and/or PVT. Malignant form of PES in RVOT could partially depend on the localization of its origin.

P4095 Effect of vagal nerve on the monophasic action potential of ventricular outflow tract
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Objective: Vagal nerve may be related with idiopathic ventricular tachycardia (VT). The present study was aimed to investigate the effect of vagal nerve on the monophasic action potential (MAP) of ventricular outflow tract.

Methods: Eight adult mongrel dogs were involved. Bilateral vagosympathetic tensors were decentralized for stimulation. Metoprolol was given to block sympathetic effects. Three MAP recording electrode were placed at the left ventricular outflow tract (LVOT), right ventricular outflow tract (RVOT) and right ventricular apex (RVA) respectively through right femoral artery and vein. MAP was recorded at the LVOT, RVOT, RVA with or without vagal stimulation (VAS) respectively.

Results: MAPD at LVOT was thinner than that at RVOT and RVA with or without vagal stimulation (VAS) respectively. In pts referred for frequent PVC ablation, electromechanical coupling interval of the PVC was significantly shorter in pts with VAS compared to those without VAS. PVC originated from posterior, free wall in 7 out of 9 patients in M-gr, and 1 out of 21 patients in B-gr (p < 0.01).

Conclusion: VS could reduce MAPD significantly. With VS, the abbreviation of MAPD at outflow tract was shorter than that at RVOT and LVOT (P < 0.05), while there was no difference of MAPD at LVOT vs 8.3 ± 5.5 at RVOT and LVOT. With VS, the abbreviation of MAPD at RVA with or without vagal stimulation (VAS) respectively.

P4096 Electromechanical coupling interval: a new marker of PVC in LV dysfunction

Introduction: Mechanisms responsible of PVC-induced left ventricular (LV) dysfunction are not fully understood. We studied whether the electromechanical coupling interval (ECLI) to the preceding cardiac cycle and other characteristics of the PVC are associated with LV dysfunction.

Methods: We prospectively included 29 patients (pts) (55±16 years, LV ejection fraction (LVEF) 41 ±17% and 62% male) with frequent PVC (10% in 24 hours Holter) referred for ablation from 2009 to 2011. Electromechanical coupling interval was estimated as the interval between dicrotic notch in the pulse wave and onset of PVC. Site of origin of PVC, percentage of PVC, percentage of pts with interpolated PVC, electrical coupling and electromechanical coupling interval were measured.

Results: 11 pts (38%) had reversible cardiomyopathy (basal LVEF 30% [24-35%] and 6 month LVEF 47% [40-51%], p < 0.01). 18 pts (61%) had normal heart. There were no statistical differences on site of origin of PVC (right ventricular outflow tract 33% vs 66%, left ventricular outflow tract 62% vs 37%, others 33% vs 66%, p=0.48), percentage of PVC (15% [11-49%] vs 12% [10-43%] per 24 hours, p=0.30), percentage of pts with interpolated PVC (27% vs 16%, p=0.77) and electrical coupling (504 ms [455-565 ms] vs 465 ms [412-696 ms], p=0.77).

Electromechanical coupling interval of the PVC was significantly shorter in pts with PVC and LV dysfunction (24 ms [6-00] vs 89 ms [55-216 ms], p=0.01) and show a better correlation than electrical coupling interval with basal LVEF (r=0.46, p=0.045).

P4097 Digitalis use and multivessel disease independently predict ventricular fibrillation at reperfusion in PCI-treated patients with STElevation myocardial infarction
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Purpose: Ventricular fibrillation (VF) during reperfusion in ST-elevation myocardial infarction (STEMI) is an infrequent event, but confers increased in-hospital mortality. We assessed clinical characteristics associated with VF during reperfusion in an unselected population of STEMI patients treated with percutaneous coronary intervention (PCI).

Methods: It total, 1744 consecutive STEMI patients were admitted to a Swedish tertiary care hospital for primary PCI during 2007-2009. Clinical characteristics and information about presence of VF were obtained from the Register of Information and Knowledge about Swedish Heart Intensive care Admissions. Medical records were reviewed to determine VF timing in relation to the infarct-related artery (IRA) opening. Clinical and angiographic characteristics were tested for association with reperfusion VF using logistic regression analysis.

Results: Digital (IRA) occlusion was present in 1127 patients (66±12 years, 72% male) at admission, of whom 26 (2.3%) developed VF at IRA opening. Increased risk of VF during reperfusion was observed for aspirin, beta-blockers or digitalis at admission, VF before reperfusion, inferior location of infarct and multivessel disease. In multivariate analyses, only multivessel disease and the use of digoxin remained independently associated with reperfusion VF (Table). Reperfusion VF was not associated with either age, gender, body mass index, history of hypertension, heart failure, diabetes, stroke, PCI, CABG, myocardial infarction, IRA or the presence of left main artery stenosis.

Conclusion: Multivessel disease and digitalis use at admission independently predict VF at IRA opening in patients with acute STEMI. Our data further support a proarrhythmic effect of digitalis in the setting of acute coronary syndrome.

P4098 Electroanatomical substrate mapping guidance for left ventricular aneurysmectomy in patients after myocardial infarction
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Introduction: Left ventricular aneurysmectomy (LVAR) with peri-infarct cryoablation...
is an effective approach for the treatment of post-MI patients who present with VT. The purpose of this prospective study was to evaluate the efficacy of catheter-based electroanatomical mapping (EAM) prior to aneurysmectomy to identify the arrhythmogenic zones as a guide for surgical resection and efferent vessels construction. Method: We included 35 pts (MF: 28/7), average age 64 years (38 – 79). Mean LVEF prior the surgery was 23.5% (20-50%) and post MI aneurysms were documented by echocardiography or LV angiography. VT inducibility was confirmed prior to surgery and EAM was performed (CARTO, Biosense-Webster) to identify border zones and lateral/fractionated potentials. The surgeon used the EAM image during surgery. Arrhythmogenic zones were eliminated by aneurysmectomy, endocardial resection and cryotherapy. An EP study and EA mapping were repeated – at 3 mo after surgery.

Results: In 27 pts we performed LVAR + CABG, in 5 pts LVAR + mitral valvuloplasty and in 3 pts LVAR + cryotherapy. The EF improved significantly to 48%.

Conclusions: EA mapping prior to LVAR can facilitate arrhythmogenic substrate elimination with significant reduction of VT induction – this minimizes the risk of life threatening arrhythmias.

P4099 Increased spatial dispersion of the ventricular recovery time in patients with idiopathic ventricular fibrillation

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Background: Diagnosis of idiopathic ventricular fibrillation (IVF) before its occurrence is very challenging, because cardiac arrest could represent the first or the only sign of the disease. Heterogeneity of ventricular repolarization has been consistently reported to be linked to ventricular tachycardia in patients with ischemic and idiopathic cardiomyopathy. The purpose of this study was to test the hypothesis that IVF also might be associated with ventricular repolarization abnormalities.

Methods and Results: Spatial dispersion of recovery time as an index of heterogeneity of ventricular repolarization was assessed by means of a 187-channel signal-averaged vector-projected high-resolution electrocardiograph (187-ch SAVP-ECG) in a group of 14 consecutive patients (13 male, 48 ± 17 year-old) who were diagnosed with IVF and who received ICDs for secondary prevention after an episode of resuscitated sudden cardiac death. A control group consisting of 22 healthy persons (22 male, 35 ± 7 year-old) was set for comparison. Recordings took a maximum of 10 minutes and were obtained without any complication. The patients with IVF did not present with characteristic ECG abnormalities. Spatial dispersion of corrected recovery time (defined as the time between the R wave peak and the first positive maximum derivative of T wave corrected by Bazett’s formula) was significantly higher in the IVF group compared with the control group (94 ± 17 milliseconds versus 63 ± 17 milliseconds P < 0.001).

Conclusions: 187-ch SAVP-ECG is a simple and reliable method for the evaluation of ventricular repolarization. It may be useful to reveal patients with latent IVF.

P4100 Predictors and prognosis of ventricular fibrillation during acute coronary syndromes


Introduction: Different types of arrhythmias are originated in the setting of acute coronary syndromes (ACS) due to electrical instability and ischemia. The most important is ventricular tachycardia which degrades in ventricular fibrillation (VF). VF during hospital stay is associated with a poor prognosis.

Objective: Assess the predictors and prognosis of VF during ACS.

Methods and results: We performed a prospective study involving 902 consecutives patients (P; aged 64±13.2 years, 77.5% male) admitted in a Coronary Unit for the first 2 years with a 6 months follow-up. The VF rhythm was identified in 51 P (5.7%) during hospital stay. This arrhythmia was not associated with any cardiovascular risk factor, relevant past medical history (including ischemic cardiomyopathy or valvular heart disease) or previous medical therapy. At admission, the P with VF presented with higher heart rate (HR; p=0.014) and lower systolic blood pressure (SBP; p<0.001). ACS with ST segment elevation was the most common type of ACS in those P (p<0.001). During hospital stay, VF was more frequent in P with multivessel disease (2 or 3 vessels, p=0.008), higher maximum Kllip class (Kllipmax; p<0.001) and left ventricular ejection fraction ≤ 40% (LVEF≤40%; p<0.001). After admission, LVEF ≤ 35% was associated with high risk for recurrent VF (p<0.001). Concerning laboratory parameters, superior medium values of C reactive protein at admission (p=0.001) and peak creatinine during hospital stay (peakcreat; p=0.001) were recorded. Mean values of NT-proBNP and cTNT were not statistically different. Pts with aggressive therapies, including intronic agents (p<0.001), intra-aortic balloon pump (p=0.009) and mechanical ventilation (p=0.001) in multivariate analysis, HR at admission (OR 1.03, 95% CI 1.01-1.05), SBP at admission (OR 0.98, 95% CI 0.96-0.99), Kllipmax→1 (OR 4.15; 95% CI 1.60-10.73) and AV block > 2 (OR 6.82; 95% CI 2.37-19.57) remained independently associated with VF. VF was predictor of death during hospital stay in univariate (p<0.001) and multivariate analysis (OR 6.64; 95% CI 1.87-23.64), and adjusted for other recognized prognostic factors (age, diabetes, LVEF≤40%; Kllipmax→1, NT-proBNP and peakcreat). Throughout follow-up, VF was not associated with death or other major adverse cardiovascular events (MACE).

Conclusion: VF is a serious arrhythmia associated with ACS. It carries worse clinical manifestations and prognosis during hospital stay, but seems to not imply continuing risk over time.

P4101 Circulating biomarkers of extracellular matrix remodeling are associated with ventricular arrhythmia in heart failure patients

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Background: Ventricular arrhythmia is a major contributor to cardiovascular mortality in heart failure (HF) patients. At the molecular level, arrhythmia is associated with extracellular matrix (ECM) remodeling. The aim of this study was to assess the correlation between circulating biomarkers of ECM and ventricular tachycardia/ fibrillation in ischemic and non-ischemic heart failure patients carrying an implantable cardioverter defibrillator (ICD).

Methods and Results: Blood samples were obtained from 90 HF patients (left ventricular ejection fraction (LVEF) = 32±9%) with an ICD and it was analyzed for ECM proteins and CRP as control. Healthy volunteers (LVEF > 60±2%; n = 10) served as control group. C-reactive protein (CRP) did not differ between groups, excluding acute inflammatory response being a potential proarrhythmic trigger. Ventricular tachycardia/fibrillation were assessed using stored ICD electrograms. Increased levels of osteopontin, matrix metalloproteinase (MMP)-2, MMP-7, MMP-9, and N-terminal brain natriuretic peptide (NT-proBNP) were detected in all heart failure patients, whereas circulating tenascin-C was reduced compared to healthy controls. With respect to the biomarker levels, ventricular tachycardia (VT) or fibrillation (VF) among heart failure patients was associated with elevated MMP-7 and NT-proBNP levels compared to the heart failure patients without ventricular tachycardia. Considering the best performance of biomarker predicting VT/VF in heart failure patients, logistic regression analysis identified osteopontin and MMP-9 as strongest predictors of HF-associated ventricular arrhythmia after adjustment for gender and β-blocker treatment.

Conclusions: Heart failure correlates with elevated circulating biomarkers of extracellular matrix remodeling. Monitoring of plasma osteopontin and MMP-9 may contribute to ventricular arrhythmia risk stratification in HF patients.

P4102 Efficiency of ICD therapy in high-risk children with Long QT syndrome

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Long QT syndrome (LQTS) is an inherited disorder caused by mutations of the genes encoding cardiac ion channels. Affected patients are characterized by increased risk for polymorphic ventricular arrhythmias (PVA), aborted cardiac arrest, and sudden cardiac death (SCD). Beta-blocker therapy is considered being the most efficient therapy for patients, however it does not protect all patients. An ICD implantation is recommended for patients at high risk for cardiac events, including those who have recurrent syncpe despite beta-blocker therapy. The study aimed to describe a single-centre experience in management of patients with severe forms of LQTS treated with ICDs.

Methods and Results: The study population consisted of 30 LQTS pts from 29 unrelated families aged from 7 to 32 (mean age 16±5 years; 15 boys) from a broader group of 340 LQTS pts. Genotype was known in 16 pts (53%): 2 had compound mutations, 1 boy had compound mutation in KCNQ1 (Jervell and Lange-Nielsen syndrome –JLN), 6 pts had single mutations in KCNH2 and 2 pts had single mutations in KCNQ2. All patients had single mutations in KCNH2. Mean QTc on resting ECG was 509±36 ms. All pts except one had multiple syncpe before ICD implantation. Mean age at implantation was 12±4 years (from 4 to 18 years). Mean ICD follow-up length after the implantation was 50±18 months. Inefficient beta-blocker therapy was the major or the only indication for ICD in 24 cases (80%). Among the other indications were: high concentration of SCD cases in patients’ families (2 cases), severe bradycardia with transient AV block during 24-hours Holter monitoring (3 cases) and aborted cardiac arrest (1 case). During the follow-up, 16 pts (53%) experienced PVA during ICD follow-up; 15 pts experienced sustained VF treated with ICD shocks; episodes of spontaneously terminated asymptomatic VF were registered in 7 pts, and unsustained ventricular tachycardia - in 4 pts. Inappropriate shock (T oversensing) was registered in 1 patient. Among genotyped pts the greater number of VF was found in pts with combined mutations vs JLN. Furthermore multiple episodes of VF were registered in 3 pts with LQT1 and in 1 - with LQT2.

Conclusions: ICD implantation was needed in about 9% of children with LQTS,
Takotsubo cardiomyopathy and arrhythmic risk

Conclusions: “Takotsubo” cardiomyopathy (TTC) is a recently described cardiac syndrome, usually triggered by intense emotional and/or physical stress, characterized by transient severe localized left ventricular dyskinesia and changes of ST segment that can mimic acute myocardial infarction, without significant coronary artery stenoses. Although the prognosis is considered good, TTC is associated with significant alterations of the QT interval that could trigger life-threatening cardiac arrhythmias. The aim of our study was to assess the extent of the alterations of the QT interval and the arrhythmic risk associated with this disease.

Methods: From August 2008 to December 2011 we prospectively enrolled all patients (pts) admitted to our Department of Cardiology (817). Myocardial fibrosis was also significantly observed in VT/VF group more than non-VT/VF group (P=0.03). The grade of MVO and amyloid deposition of peri-coronary neurons tended to be higher in VT/VF group.

Conclusion: VT/VF in amyloidosis may depend on the degree of amyloid deposition and myocardial fibrosis. Ischemic change by MVO and coronary spasm by amyloid deposition of peri-coronary neurons might lead to VT/VF.

J waves in the early recovery phase of acute myocardial infarction and its clinical implication

Methods: In 152 consecutive patients with acute MI, electrocardiogram (ECG) was monitored for one week after coronary intervention for revascularization. The all-located ECG performed during hospitalization and calculated maximum QT interval (QTmax), maximum corrected QT interval (QTcmax) and maximum QT dispersion (QTdmax). We histopathologically investigated about cardiac weight, micro vessel obstruction (MVO) in myocardium, amyloid deposition of peri-coronary neurons in epicardium, and myocardial fibrosis. Percentage of MVO numbers due to amyloid deposition was counted microscopically, and scored 3 (over 50%), 2 (25-50%), 1 (under 25%), 0 (0%). Myocardial fibrosis was assessed in one-to-four grading by Masson staining.

Results: Cardiac weight was 579±94 g in VT/VF group and 406±81 g in non-VT/VF group. Cardiac weight of VT/VF group was significantly larger than non-VT/VF group (P=0.0142).

Conclusions: Our study confirmed abnormal prolonged QT intervals and QT dispersion in pts with TTC. We found a significant incidence of ventricular arrhythmias. The pts with ventricular arrhythmias had significantly higher values of QTcmax.

J waves in the early recovery phase of acute myocardial infarction (MI) were investigated in the conducted beats of atrial premature beats.

Methods: From 01/09/2009 to 31/08/2010, we analysed 8826 standard resting 12-leads ECG of AM (77.2% male, mean age male: 36.8±10.2 yo, mean age female: 30.5±8.7 yo), including deployed fighter pilots. Prevalence of ER was 2.84% [N=251 (231 male = 92.1%, female = 7.9%), 165 in inferior leads (65.7%), 89 in lateral leads (39.4%), 13 in both (5.1%), 210 slurring pattern (83.6%), 92 notching pattern (36.6%), 51 both pattern on same ECG]. J wave was > 2.5 mm in 12 ECG (4.7%), 2-2.5 mm in 40 (13.9%), 1.5-2 mm in 72 (28.6%), 1-1.5 mm in 123 (49%).

Conclusion: Our results are closed to the results of the most recent studies. Moreover among our AM, no cardiovascular event occurred. All AM were very young, including deployed fighter pilots. Prevalence of ER was significantly higher than that observed in the age and sex comparable subjects. The specific conditions of combat flights (accelerations more than +9Gz and a speed of application up to 6 Gz/s) induce some important cardiac constraints in these pilots, leading to variations in electrophysiological conditions, vaso-vagal balance, refractory periods ... Consequently, a severe arrhythmia can be favoured in a pilot with a non-structurally or a non-electrophysiologically normal heart.

Methods: AM (military and civilian jet and transport crew) are periodically examined for fitness assessment at the same health care center (CPFT) with a standard 12-leads ECG at each visit. All ECG were independently evaluated in random order by two physicians using the definition of ER without using computerized analysis.

Results: The prevalence of J wave was 0.10%.

Conclusions: The association between early repolarization pattern (ER) and cardiac mortality remains discussed. However, in aviation medicine the risk of sudden death related to ventricular arrhythmias in Aircrew Members (AM) with ER remains a matter of concern. Particularly, fitness assessment in this situation is not easy to take for the fighter pilots who are involved in military operations, flying above hostile countries (Afghanistan, Libya ...) alone in their fast jets. Moreover, the specific conditions of combat flights (accelerations more than +9Gz and a speed of application up to 6 Gz/s) induce some important cardiac constraints in these pilots, leading to variations in electrophysiological conditions, vaso-vagal balance, refractory periods ... Consequently, a severe arrhythmia can be favoured in a pilot with a non-structurally or a non-electrophysiologically normal heart.

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How do female electrophysiologists deal with gender differences in radiation exposure during pregnancy? Results from the EPIC global survey

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Background: Awareness of radiation exposure is variable among different settings of practice in invasive electrophysiology (EP) laboratories around the world.

Methods: As part of a web-based questionnaire on individual practices focusing on radiation exposure during invasive EP procedures, a total of 8 questions were aimed specifically at female cardiologists.

Results: A total of 165 physicians (50% female) responses were received with the majority of them located in the US (38%), Canada (8%), Italy (7%) and Germany (6%)(see Table 1). When asked; “Do you consider your radiation exposure during EP procedures to be noticeable or significant (p-value)?” 39% considered it noticeable or significant. Nearly 80% of participants were cardiologists for more than 3 years (45% for more than 10 years). Of the 50 female participants, 18 were pregnant at some time during their training or during their career as electrophysiologists.

Conclusions: The baseline prevalence of RBBB and LAHB was a determining factor influencing the proliferation of HV electrograms immediately after CoreValve implantation. In addition, annulus size, the sinus of Valsalva diameter and annulus prosthesis size ratio may all influence the increments in intracardiac electrograms and PR intervals. These changes do not seem to influence the need for pacemaker implantation.

Remote navigation and electroanatomical mapping using 8-electrograms on the Maverick catheter: a validation on human subjects

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Purpose: Remote catheter navigation is a promising area of development. A novel system based on rapidly changing magnetic forces generated by electro-magnets may overcome the slow movement of a previous system based on permanent magnets. The aim of this study was to prove the accuracy and safety of the system for the human being.

Methods: This device is composed of 8-electromagnets placed around the patient’s thorax which can be remotely controlled from a console and provide 0.14 Tesla magnetic force to the tip of a magnetic catheter. The system eliminates virtually any delay for real time navigation. Consecutive patients scheduled for either supraventricular or ventricular tachycardia ablation were enrolled in the trial. Atrial flutter or atrial fibrillation criteria or ischomic ventricular tachycardia (VT) as the primary arrhythmia to ablate, presence of a pacemaker, ICD, or a prosthetic valve in the chamber to map and unstable clinical condition. Sites within the 4 chamber areas (9 in each atria, 6 in the right ventricle and 5 in the left ventricle) were considered for ablation. Remote navigation from the console in the “operator” mode. Afterwards, attempts were made to reach the same anatomic sites using the “automated” mode twice, i.e., the catheter was navigated to the same site without operator intervention.

Results: 40 patients were enrolled (age 50±17 years, 30 males). The mapped arrhythmia substrate was AV nodal reentrant tachycardia in 12, accessory pathway in 12, atrial flutter in 10, atrial fibrillation in 7 and ventricular tachycardia in 3 patients. Ventricular and atrial sites (143 cardiac chambers, 9 in each atria, 6 in the right ventricle and 5 in the left ventricle) were considered for ablation. Ventricular and atrial sites (143 cardiac chambers, 9 in each atria, 6 in the right ventricle and 5 in the left ventricle) were considered for ablation. The catheter was successfully navigated in the manual mode to all predefined sites in 95.8% of the 653 tagged sites. The initial and final distances to the target site in the automatic mode were 39.8±21.1 and 9.9±0.9 mm. There were 2 adverse even: ischemic stroke treated with thrombolysis and a cardiac tamponade which required pericardiocentesis at the end of the procedure. Both patients with complete resolution of the complication. There were also 4 pericardial effusions and 1 AV femoral fistula which resolved spontaneously.

Conclusions: Remote catheter navigation by electromagnets is fast and accurate both by the operator and automatic modes. This novel system appears safe although there are some concerns about the safety of leaving a stiff sheath bended/rotated alone in the LA for LV mapping.
Epicardial electrophysiologic mapping of ganglioneuronal plexi for concomitant atrial fibrillation

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Purpose: Ganglioneuronal plexi (GP) are hopeful optional targets for MAZE procedure. This study was aimed to reveal and identify activity of GP by epicardial location.

Methods: Fifteen patients with concomitant atrial fibrillation underwent intraoperative epicardial electrophysiologic mapping in our institution. Autonomous GP were identified by rapid atrial pacing via a temporary pacemaker after removal of fatty epicardial tissues on the surface. A 24-point high-frequency stimulation (1000/minute, 18V) was achieved by placing tweezers directly on the left atrial epicardium. Diagram of epicardial mapping locations is shown below. (Picture)

Results: Active GP were found in 13 out of 15 patients. The incidence of activity by epicardial location is shown below. (Table)

Activity of GP by location

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<tr>
<th>Location</th>
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<td>1</td>
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<td>2/15 (13%)</td>
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<td>6</td>
<td>3/15 (20%)</td>
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Figure 1. Diagram of epicardial mapping locations

Conclusion: Active GP could be identified dominantly in the inferior right area in left atrium.

Distribution of delayed potentials on the right ventricular endocardium in patients with late potentials on signal-averaged electrocardiograms due to arrhythmogenic right ventricular cardiomyopathy

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Purpose: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a progressive inherited disease characterized by life-threatening ventricular arrhythmias, which is linked to desmosomal protein abnormality. The purpose of this study is to clarify the distribution of delayed potentials (DPs) on the right ventricular endocardium in ARVC patients with ventricular tachycardias (VT) and late potentials (LPs) after QRS segment on the signal-averaged electrocardiograms (SAECG).

Methods: The studied population comprised 46 ARVC patients (mean age 50±15.8 years, 30 males and 16 females) with sustained or non-sustained VT who underwent programmed electrophysiological study. The SAECGs were recorded during sinus rhythm. LPs were defined positive when two of three parameters (total filtered QRS > 120 ms, root mean square voltage of the last 40 ms < 12 µV and duration of the low amplitude signals in the terminal portion of QRS > 38 ms) were fulfilled and low amplitude signals were noted on SAECG during period consistent with ST segment in simultaneously recorded orthogonal XYZ ECGs. The distribution of DPs, fractionated electrograms, and double-potentials in the right ventricle (RV) evaluated by detailed endocardial mapping (3D electroanatomical voltage mapping and conventional mapping) during sinus rhythm was compared with the outcome of catheter ablation.

Results: All patients were positive for LPs on SAECG. 37 of 46 patients (80%) had DPs, although they were not obtained in the remaining 12 patients (20%). DPs were located in the RV basal area (100%), particularly in infarct wall in 30 patients (81%), RV posterobasal wall in 17 patients (46%), RV lateral/basal wall in 20 patients (54%), anterobasal wall and/or RV outflow tract (RVOT) in 7 patients (19%) and RV basalseptum in 8 patients (22%). They were distributed in the RV mid to apical area in only 2 patients (5%, P < 0.01). VT was eliminated by endocardial catheter ablation in 24 (83%) of 29 patients with inducible VT by programmed electrical stimulation. DPs were mainly located in the infarct area in 20 (63%) of 32 successful patients. Distribution of fractionated electrograms or double-potentials was not predictable for successful ablation site.

Conclusions: In ARVC patients, DPs were mainly located in the basal RV wall especially in the inferior region around tricuspid valve annulus. We conclude that catheter ablation following endocardial mapping should be applied first in the RV infarct wall in patients with LPs on SAECG.
Cavotricuspid isthmus radiofrequency catheter ablation (CT RFA) is recommended for typical atrial flutter since it is safe and effective to maintain sinus rhythm, but the long-term outcomes have not been compared with those in patients with other types of atrial arrhythmia and/or other management. This study investigated the outcomes after CT RFA for atrial flutter, expected to maintain sinus rhythm and possibly to reduce mortality and morbidity.

**Methods:** We examined the clinical course of 8,962 consecutive patients with atrial fibrillation and/or atrial flutter. The outcomes in 875 patients with CT RFA for typical atrial flutter (in whom 32% had a pre-ablation history of atrial fibrillation) were compared with those in other patients.

**Results:** Complete cavotricuspid isthmus block was successfully obtained in 97% of the patients. Median follow-up was 934.1±113.4 days. Death (n=1,155), stroke/thromboembolic events (n=715) or bleeding events (n=791) were recorded in 2,035/8,962 patients. Kaplan-Meier analysis showed that patients who underwent RFA had longer survival than other patients (p<0.0001) and higher net clinical benefit (freedom from combined death, stroke, thromboembolic and bleeding events, p<0.0001). Using cox proportional-hazards model, results remained significant after adjustment for age, CHADS2 and HAS BLED scores, use of cardiovascular medications and other confounders. Patients in the ablation group revealed lower risk of all-cause mortality (hazard ratios [HR] = 0.56, 95% confidence interval [CI], 0.40-0.78; p=0.0007), of stroke/thromboembolic events (HR=0.60, 95% CI, 0.41-0.91; p=0.001) and of bleeding events (HR=0.71, 95% CI, 0.52-0.96; p=0.03), resulting in a significant net clinical benefit (HR=0.67, 95% CI, 0.54-0.83; p=0.0002).

**Conclusions:** Atrial flutter with CT RFA is independently associated with a lower mortality and morbidity as compared with other sustained atrial arrhythmias such as atrial fibrillation.

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**P4114**

**Use of Wearable Cardioverter Defibrillator after implantable cardioverter defibrillator explanation: clinical experience from 151 German patients**

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**Purpose:** Several studies and case reports have described successful use of the wearable cardioverter defibrillator (WCD) for protection from sudden cardiac death (SCD) among European patients. We sought to evaluate the experience with the WCD in German patients whose implantable cardioverter defibrillators (ICDs) had been explanted or deactivated.

**Methods:** Patients who were prescribed a WCD due to ICD explantation or deactivation between 2009 and 2011 in Germany were retrospectively analyzed in our study. We reviewed medical charts to collect demographic information, primary reason for ICD implantation, and primary reason for ICD explantation or deactivation. Patients’ duration of WCD use and electrocardiogram (ECG) from device recording were gathered from the manufacturer’s post-market database.

**Results:** 151 German patients (male = 86.7%, mean age=61.1±11 years) underwent ICD explaination (n=150) or deactivation (n=1). 45.0% of patients received an ICD for primary prevention, 19.2% for secondary prevention, and 35.8% not available during chart review. Infection was the major reason for ICD explantation (80.1%), followed by lead defect (19.9%), radiotherapy (0.6%), and reasons for ICD explantation were not specified for 14.3% of patients. Patients were monitored on average of 52.38 days (median=44, ranging from 1 to 225 days); the average daily use was 20.6±4.2 hours. One patient experienced a sinus arrest and recovered spontaneously. Two others who received ventricular tachyarrhythmia arrest and were successfully treated by the WCD with single 150 joule shocks. Both patients were unconscious during the episodes, survived acutely, and had ICD re-implanted afterwards.

**Conclusions:** In German patients with ICD explantation or deactivation, the use of a WCD was effective for protection from SCD (1.0% per patient-month); WCD was an effective bridge for protection from SCD when the ICD therapy was discontinued. Compliance among the patients was high.

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**P4115**

**Precise value of programmed ventricular stimulation in ischemic cardiomyopathy and dilated cardiomyopathy patients with preserved systolic function**

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**Purpose:** Up to date, programmed ventricular stimulation (PVS) is not considered as a reliable risk stratifier for primary prevention of sudden cardiac death in patients with structural heart disease and preserved systolic function. The objective of the present study is to investigate the prognostic value of PVS in ischemic cardiomyopathy (ICM) and dilated cardiomyopathy (DCM) patients with left ventricular ejection fraction (LVEF) >40%.

**Methods:** We followed up for a mean period of 52.4 months 76 patients with ICM and 39 with DCM (65.9 years old, mean LVEF=45.5%). All patients underwent PVS based on the presence of syncope or non sustained ventricular tachycardia in an ambulatory setting. Stimulation protocol consisted of up to triple extrastimuli and 200 ms atrial fusion. The arrhythmia induced was defined either as sustained monomorphic ventricular tachycardia (VT) or polymorphic VT leading eventually to VF (ventricular fibrillation).

**Results:** Sustained monomorphic VT or VF was triggered in 40 cases (30/76 of ICM patients and 10/39 of DCM patients) and subsequently implantable cardioverter defibrillators (ICD) were implanted in 36/40 of these patients. During the follow-up period, 7 patients died; 2 experienced sudden cardiac death and 5 non cardiac death. Although no difference was observed between patients with VT/VF induction and those without in the incidence of total mortality (10% vs. 4%, log rank p=0.20), the incidence of sudden cardiac death was higher in the former group (5/35 vs 2/31 patients, log rank p=0.05), indicating an absolute negative prognostic value of PVS for patients without VT/VF induction. Appropriate ICD activation was observed in 24 patients (66.7%) with VT/VF induction was (21 cases with antitachycardia pacing, 16 with shocks, 13 with both) and the time for the first appropriate activation was 23 months after ICD implantation.

**Conclusion:** During long-term follow-up, DCM and ICM patients with preserved systolic function and VT/VF inducibility experienced a significant incidence of appropriate ICD therapy. Additionally, SCD was absent in non inducible patients with structural heart disease. PVS may be considered as a reliable risk stratifier for primary prevention of sudden cardiac death in high risk patients with structural heart disease and preserved systolic function.

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**P4116**

**Return of spontaneous circulation after unwitnessed out-of-hospital cardiac arrest with asystole on initial rhythm**

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**Objective:** To determine the pre-hospital variables which have significant impact on ROSC after unwitnessed OHCA in patients with asystole on initial rhythm.

**Methods:** Of 522,801 resuscitation-attempted adult patients with OHCA, 141,379 bystander-unwitnessed arrests of presumed cardiac origin were analyzed in a prospectively recorded nationwide Utstein-style database in Japan over 5 years (2005–2009). The primary endpoint was ROSC before arrival to hospital that represents the earliest endpoint reflecting the “unbiased” initial resuscitation success. The second endpoint was 1-month survival with favorable neurological outcome (cerebral performance category scale = 1 or 2).

**Results:** Overall ratio of 1-month survival and that with favorable neurological survival were 0.64% (n=801) and 0.15% (n=211), respectively. ROSCs were achieved in 1,010 patients before arrival to hospitals. The incidence of ROSC was higher in men than in women (men: 0.78%, women: 0.64%; p < 0.002). The age was younger in ROSC group than in non-ROSC group (ROSC group: 74.3±13.5 years, non-ROSC group: 76.4±13.8 years; p < 0.0001). The percentage of administration of automated external defibrillator (AED) before arrival to hospital was higher in ROSC group than in non-ROSC group (ROSC group: 6.9±3.5 minutes, non-ROSC group: 7.3±3.7 minutes; p < 0.0001). Multivariate logistic regression analysis revealed that the following independent factors were found to have a significant impact on the probability of ROSC before hospital arrival (incident ratio, 1.00-1.99), call-response time interval (unit OR, 0.99 to 1.00), call-response time interval (unit OR, 0.97; 95% CI, 0.95 to 1.03), and pre-hospital administration of AED (OR, 4.49; 95% CI, 3.69-5.41).

**Conclusions:** Pre-hospital variables (age, call-response time interval, and administration of AED) were crucial variables for predicting ROSC after OHCA with asystole on initial rhythm. This was true even in patients with asystole on initial rhythm after unwitnessed OHCA. ROSC will be achieved if patient is younger, call-response time interval is shorter, and AED is administered before arrival to hospital.
Long-term follow-up and predictors of arrhythmic events in the brugada registry of the piedmont region of Italy

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Introduction: Brugada syndrome is an arrhythmogenic disease characterized by increased risk of sudden death (SD) and so far the only proven therapy is the implantable cardioverter defibrillator (ICD), although there are some evidence in favor of hydroquinidine. The question of risk stratification in patients with Brugada ECG pattern, especially if asymptomatic, remains still very controversial. The aim of our study is to analyze the long-term prognosis and the role of clinical and electrophysiological risk factors in the Brugada Registry of Piedmont Region in Italy.

Methods and results: Four hundred and eighteen patients with spontaneous or drug-induced type 1 Brugada were enrolled consecutively. 2/3 of all patients were admitted to the san Luigi hospital in Turin, 1/3 were in the emergency network. Syncope (p<0.001) and positive PES with up to 2 extrastimuli were the only predictors of events. In the asymptomatic group, no independent risk factors were identified. Predictors of arrhythmic events in the whole population were: Asymptomatic; age >50 years (p=0.001); AVB; QRS <120 ms (p=0.001); RBBB (up to 1/3 in patients with AVB, 7% vs 13% in those with HB); family history of SD. Only induction with protocol A was predictive of events at follow-up (p=0.007). Nor spontaneous type 1 ECG, nor a VRP ≥200 ms were predictive of events. In the asymptomatic no independent risk factors were identified.

Conclusions: In the whole population of Brugada patients of the Piedmont region, only syncope and positive PES with up to 2 extrastimuli were the only predictors of arrhythmic events. No predictors of SD were identified in the asymptomatic, mainly due to the low number of events at follow-up.

Abstract P4119 — Table 1. AED dissemination during 2005-2010

<table>
<thead>
<tr>
<th>Year</th>
<th>2005</th>
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<th>2009</th>
<th>2010</th>
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<td>No of AEDs available in public</td>
<td>1274</td>
<td>1276</td>
<td>1556</td>
<td>1744</td>
<td>1903</td>
<td>2052</td>
<td>NA**</td>
</tr>
<tr>
<td>No of public AEDs available in public centers</td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>36</td>
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<td>36</td>
</tr>
<tr>
<td>AEDs per square Km</td>
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<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>OHCA high-incidence areas covered by AED, n (%)</td>
<td>4 (3.5%)</td>
<td>19 (19.9%)</td>
<td>25 (25.1%)</td>
<td>40 (35.1%)</td>
<td>40 (35.1%)</td>
<td>40 (35.1%)</td>
<td>40 (35.1%)</td>
</tr>
<tr>
<td>OHCA covered by nearby AED, n (% of all OHCA)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Conclusion: Despite the clear usefulness of ECG in the diagnosis of SD cases, it can be normal or unspecific in an important percentage of patients. In this sense, SD screening programs that include only a baseline ECG, could lead to a loss of sensitivity. A comprehensive study including cardiac imaging and genetic information, are also important besides ECG findings to achieve a definitive diagnosis.

Abstract P4121

Association between an invasive strategy involving electrophysiologic study with prophylactic pacing and survival outcomes among adults with myotonic dystrophy type 1 and conduction system disease

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Purpose: Up to 1/3 of patients with myotonic dystrophy type 1 (DM1) die suddenly. No intervention has thus far, effectively prevented sudden death (SD) in DM1. Our objective was to determine whether an invasive strategy (IS) based on electrophysiological study (EPS) and prophylactic pacing if HV interval is >70 ms, prolongs the survival of patients with DM1.

Methods: Between January 2000 and December 2009, the DM1 Heart Registry included 914 patients suffering from DM1 in 71 Pitie-Salpetriere Hospital, among 486 patients whose electrophysiological test showed a PR interval >200 ms, a QRS duration >100 ms, or both, we compared overall survival (primary outcome measure) and SD, respiratory death and other deaths (secondary measures) of 341 patients who could be treated with an AED had grown more than 6-fold from 11 (0.7%) to 91 (4.4%), in the same period.

Conclusion: Initiative for strategic placement of publicly available AEDs has increased coverage of OHCA high-incidence areas substantially, hereby raising the potential number of patients who could be treated with an AED and save additional lives.
Cardiac conduction system involvement in patients with steinert's myotonic dystrophy

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Introduction: Steinert’s myotonic dystrophy (DM1) is an autosomal dominant genetic disease: male/female ratio is 1:1 and an affected parent has a 50% risk of transmitting the disease in each pregnancy. In Europe and North America it is the most common muscular dystrophy (1:8000 population). Affected patients have a lower life expectancy with an average age of death of 53 years and there is a correlation between the age of onset of dystrophy and age of death: respiratory failure and cardiovascular arrest are the main causes. The cardiac involvement is quite common, especially in the conduction system, which can sometimes cause sudden death.

Methods: From January 2010 to September 2011 at our Centre 39 patients were evaluated with Steinert muscular dystrophy. The inclusion criteria was the confirmation of Steinert’s dystrophy by genetic analysis and clinical examination. The evaluation of muscle strength with MRS (muscular impairment rating scale).

Results: 39 patients were evaluated: 21 males and 18 females aged between 22 and 73 years. 23.1% (n = 9) presented family history of sudden death, while 17.9% (n = 7) reported idiopathic or syncope. PR: 0.02s was observed in 26% (n = 11) and > 0.24s in 10.3%. A PR: 0.24s, was shown to be influenced by patients’ age (p = 0.028), disease duration longer than two years (p = 0.02) and five years (p = 0.027), by severe neuro muscular involvement (p = 0.027), assisted walking (p = 0.028), evidence of obstructive lung disease (p = 0.043), presence of Supraventricular Premature Contractions, single (0.040) and couples (0.06) at Holter monitoring. Complete Left Bundle Branch Block was observed in 2 patients, and left anterior fascicular block in four (13.8%). The retrospective analysis of ECGs, disclosed an increase of PR in 20.5% of cases, and widening of QRS in 5.1%. The progression of AV conduction delay was showed to be influenced by sex (p = 0.032) and neuro muscular involvement (0.046). The development of Atrial Fibrillation was recorded in three patients. No significant abnormalities were found at Echocardiography.

Conclusions: We observed that an important involvement of the conduction system in the observed patients trends up to deteriorate quickly. Therefore it is essential that they continue to be assessed periodically. In addition to the ECG abnormalities, also other parameters seems to be associated with an increased risk of sudden death: positive family history, pulmonary involvement and degree of neuro muscular involvement.

Purpose: Sudden cardiac arrest (SCA) incidence rises with advancing age but the burden among younger individuals has greater societal consequences. Contemporaneous data on the burden of SCA is lacking. Therefore, we compared SCA incidence and survival in the community between residents ≤55 years of age and older subjects.

Methods: Complete population-based SCA incidence was prospectively identified using multiple sources in a large community in the Northwestern US (population = 630,000) between 2002 to 2005. By a detailed review of medical records and medical examiner documentation for SCA circumstances and clinical profile, only adult subjects with primary cardiac etiologies were included.

Results: Between 2002 and 2005, a total of 1,142 adult SCA cases were identified (700 males [61%]; mean age 67.15 yrs; 442 women [39%], 73.15 yrs). Nearly one quarter (256 cases, 22%) were 55 years or younger and 42% were 65 or younger with a male predominance in the younger groups and a greater proportion of females among those ≥75 yrs. Cumulative rates (%) per gender and age-group are shown in Figure. Survival rates to hospital discharge were not significantly different between subjects ≤55 and ≥55 years (7.5 vs 7.0%, P = .77; Fisher’s exact test). The race/ethnicity distribution of the population was Caucasian (63%), African American (9%), Asian (3%), Hispanic (2%), and Other (3%).

Conclusion: PCI during continued CPR can be helpful in patients with ventricular fibrillation benefit.

Purpose: Direct current shock with implantable cardioverter-defibrillator (ICD) implantation is the standard treatment for primary prevention of sudden cardiac death (SCD). The P4124 study was a prospective, single centre study to evaluate the prognostic value of procalcitonin (PCT), troponin I (TNI), myoglobin (TnM), and creatine kinase-MB (CK-MB) for prediction of survival in patients undergoing primary PCI during CPR.

Methods: 70 consecutive patients (n = 70) with out-of-hospital cardiac arrest (n = 61) were included in the study. Patients with shockable rhythms were resuscitated with CPR followed by primary PCI. Plasma samples were collected upon hospital admission and after 24 hours and 48 hours of PCI. PCT, TNI, TnM, and CK-MB were measured. The primary end point was survival at 9 years.

Results: Among patients with DM1, use of an invasive strategy compared with a non-invasive strategy was associated with a higher rate of 9-year survival. Conclusions: The proportion of subjects under age 55 among cardiac arrest victims in the community is substantial and is likely to impact great societal consequences. Especially since younger age does not provide a survival advantage, a continued focus on improved and early risk prediction of SCA is warranted.
Impacts of rewarming speed differences on outcomes of
therapeutic hypothermia in out-of-hospital cardiac arrest: is rapid rewarming efficient?

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Background: Although therapeutic hypothermia (TH) has been reported to improve neurological outcomes of patients with out-of-hospital cardiac arrest (OHCA), procedures of TH remain to be established. Particularly, rewarming speed that maximizes protection afforded by TH has not been identified.

Methods: We analyzed data from 408 patients submitted to the multicenter registry of OHCA patients treated with TH from 2005 to 2009 in Japan. The patients were retrospectively divided into three groups according to rewarming speed: 53 patients with rewarming speed 0.0-2.0°C/12 hours (Moderate group), 301 patients with rewarming speed >2.0°C/12 hours (Slow group). We defined favorable neurological outcomes as cerebral performance category (CPC) 1 or 2.

Results: There was no significant inter-group difference in gender, age, and percentages of presence of bystanders, bystander cardiopulmonary resuscitation and ventricular fibrillation in initial ECG. Incidence of return of spontaneous circulation before admission and target temperature were also comparable between the three groups, but the duration of hypothermia at target temperature in the Rapid group was shorter than that in the other groups (26±11 hours for Rapid, 35±12 hours for Moderate, 33±13 hours for Slow, p<0.01). Both the mortality and the rate of favorable neurological outcomes in 30 days were not statistically different in all three groups (Figure 1A, 1B).

Conclusion: These results suggest that benefits of TH in terms of mortality and neurological outcomes are not affected by differences in rewarming speeds. TH with rapid rewarming (≥2.0 degrees C/12 hours) appears to be as efficient as the other rewarming protocols.

Circadian variation in shockable heart rhythm and survival in out-of-hospital cardiac arrests

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Purpose: Out-of-hospital cardiac arrest (OHCA) frequency is known to have circadian variation, but little is known about whether shockable heart rhythm (VF/pulseless VT) and survival among OHCA patients also show circadian variation.

Methods: Data from all OHCA in Copenhagen were collected from 1994-2010 including age, sex, initial heart rhythm and emergency medical system (EMS) response time. Occurrence of shockable heart rhythm and 30-day survival according to time of day were analyzed by logistic regression models, adjusted for sex, age and EMS response time.

Results: Of 6,766 patients included, 70.2% suffered OHCA at home. Median age among patients with and without initial shockable heart rhythm was 66 (IQR 55-76) and 73 (IQR 60-82) years, respectively. The median EMS response time was 5.0 minutes (IQR 4-7, Figure). Daytime OHCA (7 am to 3 pm) accounted for 43.5% (n=2945), evening OHCA (3 pm to 11 pm) for 27.8% (n=2556) and nighttime OHCA (11 pm to 7 am) for 28.7% (n=1265). Compared with nighttime, daytime and evening OHCA were positively associated with shockable heart rhythm (OR 1.90, CI 1.57-2.29; OR 1.76, CI 1.45-2.13) and increased 30-day survival (OR 1.62, CI 1.18-2.22; OR 2.06, CI 1.50-2.81), despite a constant EMS response time.

Conclusion: OHCA during daytime and evening are associated with higher occurrence of shockable heart rhythm and higher 30-day survival compared with OHCA during nighttime, indicating circadian variation of these parameters, despite constant EMS response time.
## Risk factors for sudden cardiac death: Results from the Nordic arrhythmogenic right ventricular cardiomyopathy registry

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**Purpose:** Risk factors for sudden cardiac death (SCD) in arrhythmogenic right ventricular cardiomyopathy (ARVC) are not clear. We aimed to study this in a registry study of ARVC patients.

**Methods:** The study was based on a newly started Nordic ARVC registry including patients from centers in Denmark, Sweden and Norway. It was performed as a retrospective cross sectional case control study. The outcome definition was a composite as SCD, aborted SCD, or implantable cardioverter-defibrillator (ICD) shocks. The inclusion criterion was a diagnosis of ARVC according to the 2010 task force criteria (TF2010).

The following factors were studied for their association with the outcome: age, gender, history (Hx) of syncope, Hx of atrial fibrillation, inserted T waves in ECG lead V1>0.10 mV, ejection fraction (EF)<50%, right bundle branch block (RBBB), a pathogenic mutation, family Hx of sudden death, inducibility during electrophysiological study, > 500 ventricular premature complex/24H during Holter monitoring, QRS width >120 ms, peak atrial late potential on (TF2010). Hx of ventricular tachycardia (VT), being an competitive athlete, right ventricular dilatation (TF2010), left ventricular ejection fraction < 50%. All factors were primarily analyzed univariately using logistic regression, if they reached a univariate P-value < 0.05 they were secondarily studied in a multivariable logistic regression model.

**Results:** The population was comprised of 129 patients of which 57% were male and 71% probands. The median age was 48 (IQR 36-58) years and 73% had an Hx of syncope. Median retrospective follow up was 7 (IQR 4-12) years and during follow up there were 2 patients suffering SCD, 12 suffering aborted SCD, 6 patients suffering an electric storm and 25 patients experiencing appropriate ICD shocks.

Of the tested factors, epsilon waves on the ECG and Hx of VT were found to be univariately associated to the outcome. The other factors were not significantly associated. The odds ratios (OR) from the multivariable model were 3.4 (95%CI 1.2-9.7) for epsilon waves on the ECG and 8.4 (95%CI 1.8-38.6) for HX VT. They differed only insignificantly from the ones found univariately.

**Conclusions:** In this registry study of risk factors for sudden cardiac death in ARVC we found that a presence of an epsilon wave on the ECG and a history of ventricular tachycardia were associated with the composite outcome of sudden cardiac death, aborted sudden cardiac death, electrical storms and appropriate ICD shocks.

## Survival from inpatient cardiac arrest in a referral hospital for cardiology and cardiovascular surgery

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**Purpose:** We sought to estimate survival from inpatient cardiac arrest at the Cardiac Surgery Center, a tertiary referral hospital for cardiology and cardiovascular surgery.

**Methods:** We recorded cardiac arrests over a 48-month period, using the Utstein style of recording data for cardiac and surgical patients, who are distributed on 3 inpatient floors. The arrival time of the cardiac arrest team (CAT) was calculated according to the 2010 task force criteria (TF2010). The following factors were studied for their association with the outcome: age, gender, history (Hx) of syncope, Hx of atrial fibrillation, inserted T waves in ECG lead V1>0.10 mV, ejection fraction (EF)<50%, right bundle branch block (RBBB), a pathogenic mutation, family Hx of sudden death, inducibility during electrophysiological study, > 500 ventricular premature complex/24H during Holter monitoring, QRS width >120 ms, peak atrial late potential on (TF2010). Hx of ventricular tachycardia (VT), being an competitive athlete, right ventricular dilatation (TF2010), left ventricular ejection fraction < 50%. All factors were primarily analyzed univariately using logistic regression, if they reached a univariate P-value < 0.05 they were secondarily studied in a multivariable logistic regression model.

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The population was comprised of 129 patients of which 57% were male and 71% probands. The median age was 48 (IQR 36-58) years and 73% had an Hx of syncope. Median retrospective follow up was 7 (IQR 4-12) years and during follow up there were 2 patients suffering SCD, 12 suffering aborted SCD, 6 patients suffering an electric storm and 25 patients experiencing appropriate ICD shocks.

Of the tested factors, epsilon waves on the ECG and Hx of VT were found to be univariately associated to the outcome. The other factors were not significantly associated. The odds ratios (OR) from the multivariable model were 3.4 (95%CI 1.2-9.7) for epsilon waves on the ECG and 8.4 (95%CI 1.8-38.6) for HX VT. They differed only insignificantly from the ones found univariately.

**Conclusions:** In this registry study of risk factors for sudden cardiac death in ARVC we found that a presence of an epsilon wave on the ECG and a history of ventricular tachycardia were associated with the composite outcome of sudden cardiac death, aborted sudden cardiac death, electrical storms and appropriate ICD shocks.

## ECG changes during hypothermia as potential markers of mortality of successfully resuscitated patients


**Introduction:** Therapeutic hypothermia (HTH) is the therapy of choice to improve neurologic outcome and survival of patients remaining comatose after successful resuscitation. The reversible electrophysiologic changes induced by HT, e.g. bradycardia and prolongation of QT intervals, may increase the risk of malignant arrhythmias.

**Methods:** Our goal was to analyse the data of 32 patients treated with HTH in the University from 01/01/2009 to 30/11/2010. We compared the heart rate, PQ, QT, and corrected QT (QTc) intervals measured during HTH (on 32-34°C) to those of during normothermia(NT), and relationship among survival and these techniques. We used by Cox regression. The measure of the 25th and 7 female patients was 64 (SD:12) years, the mean follow-up time was 138days.

**Results:** The year survival was 40%. Between HTH and NT the following significant differences were found: heart rate: 71±21 vs 90±19 1/min; PQ: 183±32 vs 156±31 ms; QT: 488±79 vs 409±76 ms.The QRS and QTc intervals did not differ significantly. The mortality correlated significantly with the following electrophysiologic changes: the rhythm other than sinus rhythm during HTH (84.4% sinus rhythm and 15.6% other rhythm, p<0.012, HR:6.85, CI:1.02-43.08), QRS width during HTH (117.2±4ms, p=0.014, HR:1.022, CI:1.004-1.04), and QT interval during NT (159±38 ms, p=0.030, HR:1.013,CI:1.001-1.025). Two cases of ventricular fibrillation (VF) occurred during the HTH, but neither a newreversible cause nor a prolonged QTc interval were found in the background, and the presence of VFdid not influence the short-term survival.

**Conclusion:** According to our low case number study, the PQ-, QRS-intervals and the rhythm at THTmay be potential markers of higher mortality, but the ECG changes between HTH and NT did not influence the development of further VF, so HTH can be safely applied during postresuscitation care.
Copeptin predicts neurological outcomes in out-of-hospital cardiac arrest survivors

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Purpose: Prognostic stratification is fundamental for selection of the most appropriate therapeutic strategy in cardiac arrest survivors. Current evidence on prognostic markers in cardiac arrest survivors is, however, still insufficient and the data on prognostic value of C-terminal provasopressin (copeptin) in these patients are lacking.

Methods: We analyzed a group of twenty-four out-of-hospital cardiac arrest survivors. All patients were treated by endovascular hypothermia, patients with ST-elevation myocardial infarction underwent direct percutaneous coronary intervention. Copeptin levels were measured in blood samples taken at admission using commercially available immunooasay. Neurological outcome was assessed at 30 days according to Cerebral Performance Category (CPC): CPC 1 - no neurological deficit, CPC 2 - mild to moderate dysfunction, CPC 3 - severe dysfunction, CPC 4 - coma, CPC 5 - death.

Results: Fifteen patients in our group survived with good neurological outcome (CPC 1-2), five patients survived with severe neurological dysfunction (CPC 3-4), four patients died (CPC 5). Levels of copeptin were significantly lower in patients with CPC 1-2 as compared with CPC 3-4, and CPC 5 (7.7 ± 13.0 pmol/L, 251.4 ± 52.4 pmol/L, and 300.5 ± 113.4 pmol/L, respectively; P < 0.001). ROC analysis has shown cut-off copeptin value for good neurological outcomes (CPC 1-2) < 78.8 pmol/L (100% specificity, 71.8% sensitivity) and cut-off value for poor outcomes (CPC 3-5) > 170.4 pmol/L (100% specificity, 60% sensitivity). Copeptin levels significantly correlated with peak neuron-specific enolase (P < 0.05) and time to return of spontaneous circulation (P < 0.01). On the other hand, copeptin levels were comparable in patients with acute myocardial infarction and in patients with other cause of cardiac arrest.

Conclusion: Our data indicate that copeptin is a promising marker of neurological outcomes in out-of-hospital cardiac arrest survivors with significant prognostic value already at the time of hospital admission.

Detection of pulseless electrical activity by a public access defibrillator using ECG and ICG

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Purpose: Emergency pulse checks are challenging in the out-of-hospital resuscitation setting even when carried out by trained rescuers. As a consequence, current European Resuscitation Council (ERC) guidelines have eliminated pulse checks for two responders or even for minimally trained operators. A heart rate recognition system using a single-lead ECG and pulse-sensing technique, capable of automatically diagnosing cardiac arrest, together with current electrocardiogram (ECG) algorithms embedded in a Public Access Defibrillator (PAD), would aid in the management of collapsed patients. An immediate on-pad diagnosis (PAD) or stepping-up of the patient’s cardiac activity (PEA) and provide advice about cardiopulmonary resuscitation (CPR). Algorithms reported in the literature offer impressive results by coupling the ECG and ICG. However, the required analysis may not be feasible in an emergency setting, when limits the low processing power in any compact and low cost PAD.

Methods: A retrospective analysis of ECG+ICG recorded in cardiac arrest patients and controls was used to train an algorithm to detect PEA. Data were collected following ethical approval and were marked and documented by trained physicians. Segments where CPR was administered were excluded. ECG+ICG were recorded in 132 cardiac arrest patients (53 training, 79 validation) and 97 controls (47 training, 50 validation).

Results: The detection of QRs complexes in the ECG, using a modified Pan-Tompkins approach, triggers the analysis of the ICG signal in order to detect the changes that could be masked by chest wall motion. The ICG filter was used as a discriminator.

Conclusion: An algorithm to detect PEA, embedded in a compact PAD which simultaneously assesses ECG+ICG in real-time offers encouraging results.

Analysis of the relation between T-wave alternans and myocardial ischemia diagnosed by gated-SPECT: results of the SPECTACLE study

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Sudden cardiac death (SCD) concerns every year 50000 patients in France. Coronary artery disease should be responsible for 80% of SCD. There is a need to find new predictive markers of the occurrence ventricular arrhythmia, and microvolt T-wave alternans (mTWA) seems to be a promising one. The objective of our study was to analyze the relation between ischemia assessed by gated-SPECT and mTWA. Between February 2009 and January 2011, we have analyzed mTWA by Modified Moving Average method in 2235 patients, who had a myocardial gated-SPECT. Maximal mTWA was measured during pre-test, exercise and recovery phases.

Thirty nine percent (861 patients) had an ischemia and a maximal mTWA significantly higher than patients with normal myocardial perfusion: 63 [43-81] vs 54 [39-82] μV p < 0.05. Six hundred and thirty patients have had a stress induced by dipyriramole and 1605 an exercise test associated or not with dipyriramole. The mTWA distribution was the same whatever the type of stress used and whether there was a myocardial ischemia or not. Patients undergoing a gated-SPECT with dipyriramole sole have had a maximal microvolt mTWA statistically lower than the exercise group: 32 [22-47] vs 69 [52 - 90] μV p < 0.0001. The presence of ischemia under dipyriramole solely didn’t affect the level of mTWA. The analysis of the exercise population had shown that there is no difference for maximal and for exercise mTWA between the groups independently of the presence of ischemia. However there is a significant difference in recovery phase: 29 [27- 53] vs 36 [25 - 49] μV p= 0.0014 for ischemia vs no ischemia groups. The
heart rate increasing during the exercise was correlated with mTWA in recovery phase (r² = 0.22, p = 0.0001). The presence of necrosis zones has influenced mTWA in recovery phase.

To conclude, patients with ischemia in gated-SPECT seem to have a higher mTWA during recovery phase. However myocardial ischemia solely is not sufficient to induce an important mTWA.

P4138 Improved prognosis after implementation of chest compression device in out-of-hospital cardiac arrest

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Out-of-hospital cardiac arrest (OHCA) is associated with a poor prognosis. Following European Resuscitation Council Guidelines for Resuscitation 2010, application of several cardio-pulmonary resuscitation (CPR) devices may improve prognosis when used by well-trained providers. The load-distributing band (LDB) device (AutoPulse) was used for chest compressions during CPR. The aim of this study was to assess if there changed the outcomes after OHCA before and after implementation of the LDB.

Methods: The study was carried out in the Emergency Medical Services from 2009 to 2011 based on analyzing 188 emergency call-out reports. Patients were divided into two groups: 83 patients, when LDB device was used during CPR, were included in the first group (CPR-A); 95 patients were included in the second manual CPR group (CPR-M). The primary endpoint was Return of Spontaneous Circulation (ROSC) and survival to hospital admission. Groups were compared using IBM SPSS Statistics 19 software for odds ratio (OR) and relative risk (RR).

Results: We found that ROSC significantly increased after implementation of LDB device: 44 (52%) out of 83 patients of CPR-A group and 24 (25.2%) out of 95 patients of CPR-M group (OR 2.32). On the other hand the probability of an adverse outcome in the group CPR-M was higher than in patients with CPR-A (RR 1.55). CPR duration median values were: 19.5 min for CPR-A group and 28 min for CPR-M group. Among patients who survived to hospital admission, 28 (33.7%) belonged to CPR-A group, and 17 (17.9%) to CPR-M group. No significant difference was found in age, gender and cause of out-of-hospital cardiac arrest.

Conclusion: The implementation of LDB device is associated with improved ROSC and survival to hospital admission after OHCA, therefore it is expedient to apply it in pre-hospital environment.

P4139 Normal limits of the adult electrocardiogram for ages 16–90 years

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Purpose: Normal limits for the adult electrocardiogram (ECG) have been determined in a good many studies, but they all carry their imperfections: study populations are often small, they do not cover the full range of ages or give data only for one sex, or they focus on only a limited set of parameters. In this study, we established an up-to-date and comprehensive set of clinically relevant normal limits for the adult ECG, covering all ages for both sexes.

Methods: The study population included 13,364 by all evidence healthy individuals (ages ranging from 16 to 90 years, 55% men), taken from four population-based studies in The Netherlands. Standard 12-lead ECGs were available for all participants. All ECGs were processed by a well-validated computer program to obtain ECG measurements, including intervals, amplitudes, axes, and various left ventricular hypertrophy (LVH) indices. Normal limits were taken as the 2nd and 98th percentiles of the measurement distribution per age group. Additionally, continuous age-dependent percentile curves were estimated.

Results: Our study corroborates many findings of previous studies, but also provides more differentiated and detailed results, in particular for the older age groups. Age trends in normal values of the elderly were manifest for the QTc in-terval, QRS axis, and LVH indices. Amplitudes in most precordial leads of women groups. Age trends in normal values of the elderly were manifest for the QTc interval, QRS axis, and LVH indices. Normal limits were taken as the 2nd and 98th percentiles of the measurement distribution per age group. Additionally, continuous age-dependent percentile curves were estimated.

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P4140 First validation of esophageal long-term electrocardiography as an alternative technique for long-term heart rhythm monitoring

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Introduction: Diagnosing arrhythmias by conventional Holter-ECG can be cumbersome because of small p-waves, which impair visual ECG interpretation. Moreover, computer-based arrhythmia detection in continuous ECG recordings only relies on R-R-interval detection as a surrogate marker for true atrial activity. Prolonged periods of rhythm monitoring have been suggested, in particular for the detection of paroxysmal atrial fibrillation. However, longer monitoring intervals without reliable detection of true atrial activity are a limitation of techniques such as implantable loop recorders. Esophageal long-term electrocardiography (eECG) offers a way out due to the anatomic vicinity of the esophagus to the atria and its favorable bioelectric properties.

Methods: We recorded long-term eECGs from 30 subjects with a novel miniaturized ECG recorder optimized for esophageal use. The device can be worn comfortably and adherently to the ear and continuously record signals over 14 days.

Results: We found that diagnostic ECG criteria should be age- and sex-specific.

Conclusion: Esophageal long-term electrocardiography has the potential to overcome current limitations of conventional Holter-ECGs. In particular, excellent atrial signal quality will improve automatic wave detection and therefore will facilitate accurate analysis of true atrial activity.
Frontal plane ST-segment and QRS complex abnormalities as predictors of extent of necrosis and left ventricular dysfunction assessed by 3 Tesla cardiac MR

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Purpose: Some ECG changes are related to left ventricular dysfunction (LVD). Further, we have correlated the ECG findings with cardiac magnetic resonance (CMR). Our purpose was to explore the ability of the ST-segment patterns in the frontal plane compared to established data of the QRS complex to identify LVD and extent of necrosis assessed by 3 Tesla CMR.

Methods: Consecutive patients (pts) referred for 3 Tesla CMR evaluation constituted the study population. A 12-lead ECG was obtained in the same day of the CMR scan. QRS complex duration, abnormal Q waves, and ST-segment morphology (normal=upslope ST-segment; or abnormal=ST-despression or down-slope ST-segment) on leads DI or DII (the one with the largest R wave) and aVF leads were studied. These leads were selected due to the usual projection of the QRS complex and ST-segment, and to evaluate the usefulness of this simplified methodology. For detection of the presence and extent of infarcted myocardium, a breath-hold, T1-weighted, contrast-enhanced inversion recovery segmented gradient echo sequence was used. Late delayed-enhancement magnetic resonance imaging (LGE) was acquired 10 min after manual intravenous administration of 0.2 mmol/kg of gadolinium. LV end-diastolic volume (EDV) and LV end-systolic volume (ESV) were calculated using the Simpson method.

Results: Seventy consecutive patients, 48 male, mean age 64 ±15 years, were included. The most common indication for CMR was coronary artery disease and chronic valvular disease. Thirty four pts had LVD and 44 pts had LGE. QRS duration was longer in pts with LV dysfunction as compared to patients with preserved LV function (114±27 ms vs. 97±19 ms, p < 0.003). Overall, abnormal Q waves and ST-segment abnormalities had lower LV ejection fraction (43±18% vs. 56±12%, p<0.001) and larger segments of necrosis (5.4±3.5 vs. 1.5±2.2, p<0.001) than pts with normal DII-ST-segment. For LVD detection, QRS >110 ms odds ratio was 7.14 (95% CI 2.09-26.6), abnormal Q-wave was 5.92 (95% CI <2.0 to <32.0), and abnormal DII-ST-segment was 6.82 (95% CI 2.08-23.3).

Conclusions: The current hypothesis generating study demonstrates for the first time that chronic ST-segment abnormalities on DII are strongly related to LVD and to the extent of myocardial necrosis as assessed by CMR.

Epicardial cooling increases opportunity of spiral wave termination: a simulation study

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Purpose: Ventricular fibrillation (VF) is the major cause of cardiac death. There are many studies to investigate the mechanism to generate and maintain VF. However, the mechanism has not been clear yet. During VF, scroll wave rotate around a line of phase singularly called filament. Recently, increased opportunity for self-termination of VF under moderate hypothermia was demonstrated. In this study, we investigated the possibility of VF termination in a cooling heart using computer simulation.

Methods: We performed computer simulations to observe the behavior of scroll wave propagation. The left and right ventricular slab models were designed to reflect part of the ventricular wall with a thickness of 10 mm and 5 mm, respectively. The ventricular walls were composed of discrete myocardial units: 10 million units for left ventricle and 5 million units for right ventricle. The membrane kinetics in the simulated myocardium was represented by modified Luo-Rudy model. The boundary conditions in the models were used to simulate the effects of myocardial cooling. Electrical heterogeneity and rotational anisotropy through the ventricular wall were also incorporated into the model. Scroll waves were generated using an S1-S2 cross-field stimulation. Then, we simulated scroll wave reentry using nonnormality (37°C), moderate hypothermia (32°C), and severe hypothermia (27°C) heart models.

Results: The scroll wave deflection, expressed as a continuum of phase singularities, within the ventricular wall were stable, and therefore the scroll wave reentry sustained. In the case of global myocardial cooling, prolongation of action potential duration (APD) and reduction of conduction velocities were also observed. In addition, fluctuations in the filament were increased with time, and finally the scroll wave reentries were terminated. This might be due to heterogeneous increase in the APD through ventricular wall. To improve the possibility of terminating VF, we additionally simulated the effects of epicardial cooling on scroll wave behavior. When we set the linear gradient of myocardial temperature from epicardium (32°C) to endocardium (37°C), scroll wave reentry was terminated prior to the case of global myocardial cooling due to disappearance of phase singularities on epicardial surface earlier.

Conclusion: Our simulation results suggest that heterogeneous myocardial cooling from the epicardial surface can increase the opportunity of self-termination of VF.

A left-to-right interatrial frequency gradient during atrial fibrillation can be detected using standard 12-lead ECG

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Introduction: The presence of an interatrial frequency gradient may be used to guide catheter ablation of atrial fibrillation (AF). In the 12-lead ECG, Lead V1 has been shown to reflect right atrial (RA) activity, but a reliable tool for non-invasive estimation of LA fibrillatory frequency is lacking. We hypothesized that a left-to-right frequency gradient (i.e., faster fibrillating left atrium) with a frequency difference of at least 1 Hz could be detected using spatiotemporal QRST cancelation and time frequency analysis of standard 12-lead ECG.

Methods: Nineteen records from 13 patients (mean age 61±10 years, 11 male) undergoing catheter ablation of persistent AF were studied. Standard 12-lead ECG was recorded simultaneously with electrogroms from the right and left atrial appendages. AF frequency spectra were calculated from all 12 leads using spatiotemporal QRST cancelation and Welch periodogram.

Results: Mean left and right atrial appendage fibrillatory frequency was 5.6±1.2 and 2.9±1.1 Hz, respectively. Five of five cases with a left-to-right frequency gradient (100%) were identified (range 1.0 to 1.5 Hz), whereas the remaining cases either had no gradient exceeding 1 Hz (n=10) or a significant right-to-left gradient (n=4). The LA frequency component seen as a second peak in the frequency spectrum of Lead V6 in five of the 19 records. A high correlation was seen between invasively and non-invasively measured RAA frequency (r=0.94, P<0.001) and LAA frequency (r=0.91, P<0.03). Four of five cases with an invasively measured interatrial left-to-right gradient were correctly identified (positive predictive value 80%), as was 13 of 14 cases without such gradient (negative predictive value 93%) (0.05 for all cases). Indeed, pts with chronic DI-DII interatrial left-to-right gradient were correctly identified (positive predictive value 92%) and abnormal ST-segment on DI-II was 6.82 (95% CI 2.09-23.3).

Conclusions: The current hypothesis generating study demonstrates for the first time that chronic ST-segment abnormalities on DII are strongly related to LVD and to the extent of myocardial necrosis as assessed by CMR.

Role of new task force ECG criteria in the diagnosis of arrhythmogenic right ventricular dysplasia/cardiomopathy


Introduction: Former ECG signs included in the Task Force Criteria 1994 (TF94) for diagnosis of arrhythmogenic right ventricular dysplasia/cardiomopathy (ARVD/C) have been replaced by new criteria 2010 (TF10) that included the age of the probands (12 to 14 years), the extension and distribution of repolarization abnormalities in the precordial leads and the presence of intraventricular conduction abnormalities. For example, epsilon waves were added as a major sign but the presence of an S-wave < 55 ms in V1-V3 without complete right bundle branch block (RBBB) is now considered a minor sign.

Methods: We have analyzed the ECG TF10 in 47 patients with ARVD/C (66% male, 55±15 years) and compared them with the previous TF94. All of them had a complete 12-lead ECG at diagnosis, without previous arrhythmogenic or drugs or disturbances. None of them were under pacemaker therapy. ECG findings were divided into major and minor repolarization and depolarization signs according to TF criteria.

Results: The ECG was abnormal in 86% of the patients. All of them were on an ARVD/C group (mean PR interval 177±20 ms). Mean duration of the QRS complex was 107±27 ms (48% had a QRS width >110 ms, 7% an incomplete RBBB and 47% a complete RBBB). Epsilon waves were present in 23% and in a terminal S-wave <55 ms in 13% of the patients. Distribution of negative T waves in the precordial leads in the absence of RBBB was: V1-V3 (32%), V1-V3 and beyond (6%), V1-V2 (4%), and 47% had negative T waves in V1-V4 with RBBB. In 11% of the patients there were no repolarization abnormalities. TF94 major depolarization signs (epsilon waves or QRS>110ms) were fulfilled by 51% of the patients, whereas TF10 major depolarization signs (epsilon waves) were present in 29% of them (p<0.05), and 6% had minor TF10 depolarization signs. TF94 did not include major repolarization signs, and with the TF10, 38% of the patients had a major criteria. Minor repolarization criteria were present in 38% of the patients with the TF94 and in 51% with the TF10.

Conclusions: There are significant differences in ECG signs between former and new Task Force Criteria appeared in 2010. Repolarization ECG signs were present in 38% of the patients with the TF94 and in 89% with the TF10, and depolarization signs was present in 51% of the patients with the TF84 and in 36%
Role of home monitoring in effective device management of patients with implantable cardioverter-defibrillators: a prospective randomized trial

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Introduction: Telemedicine attracts the attention of health care providers and payers due to possibly increased safety and cost-effectiveness issues.

Objective: Comparison of the standard approach in the outpatient follow-up after implantation of cardioverter-defibrillator (ICD) with the remote follow-up using the access to the Home Monitoring (HM) service (BIOTRONIK) with respect to workload, efficiency and safety in ambulatory care.

Methods: 198 patients (67±12 years, 81% men) with newly implanted dual or single chamber ICD (165/35) were followed prospectively. One-third represented patients with primary prevention indications. Mean follow-up was 629±215 days. Patients were randomized to standard outpatient management (HM-) group and remotely monitored group (HM+). We evaluated regular outpatient visits, emergency visits, delivered shock therapy, and their adequacy and hospitalization associated with the ICD. Geographical data and availability of the access to the cardiological department were also analyzed.

Results: Both groups of patients were comparable with respect to the demographic data, clinical data and parameters of the ICD with significant difference only in the representation of single and dual chamber devices between the groups. Almost two-thirds of the total 621 outpatient controls were carried out in the HM-group. The number of planned inspections decreased by more than 40% in the HM-group, but the number of additional controls with the physician assistance called upon the inspection of HM messages significantly increased. Mortality did not differ significantly in both groups as well as the number of hospitalized patients and patients with delivered shock therapy. The proportion of adequate shocks, however, was significantly reduced in the HM-group.

Conclusion: Home Monitoring system proved to be effective in reducing the number of planned visits and the proportion of inadequate shock therapy with no impact on the overall mortality in our patient group. Patients with poorer accessibility of the adequate medical management tend to prefer to be monitored remotely.

IN-STENT-RESTENOSIS AND INVASIVE CORONARY IMAGING

Higher stroke rate in patients undergoing elective PCI for in-stent-stenosis in clinical practice in Europe: results of the EHS PCI registry


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Background: Although in-stent-stenosis (ISR) decreased due to better techniques, we expect significant numbers of patients suffering from ISR due to the increased overall number of PCIs. Little is known about the treatment details of ISR in elective PCI in clinical practice in Europe.

Methods: Between 2005 and 2008, 47 407 consecutive patients undergoing PCI were enrolled in the PCI Registry of the Euro Heart Survey to document patient characteristics, PCI details and hospital complications. We examined the differences in treatment of ISR versus de novo-lesions in elective PCI.

Results: A total of 22 917 patients underwent elective PCI, in 1,858 (8.0%) had ISR. Patients with ISR were younger, more often male, more often had prior MI or CABG and diabetes. They were more likely to receive unfractionated heparin rather than LMWH. No differences were found for the use of GP Iib/IIIa blockers, while bivalirudin was more frequently administered in patients with ISR. Patients with ISR got stents in 75%, of which 3/4 were DES. In patients with de novo-lesions, 95.4% received stents, with 48.3% DES. There were no differences in hospital mortality between both groups, however death/MI/Stroke was significantly higher in patients undergoing PCI for ISR (1.4% vs 0.9%).

Conclusions: Patients undergoing elective PCI for ISR were younger and had more comorbidities. They more often received DES. In hospital complications were low, however the rate of death/MI/Stroke was higher in ISR mainly due to a higher rate of stroke.

The optimal strategy for restenosis with stent fracture after drug-eluting stent implantation: 1st generation DES vs. 2nd generation DES


Background: Stent fracture is related to restenosis after drug-eluting stent (DES) implantation. As percutaneous coronary intervention (PCI) succeeds for complex lesions, increased, those for stent fracture-related restenosis also increased. However, the optimal PCI strategy for such restenosis remains unclear. We compared clinical results of PCI with 1st generationDES (zotarolimus-eluting stent, paclitaxel-eluting stent) and 2nd generation DES (zotarolimus-eluting stent, everolimus-eluting stent, biolimus-eluting stent) for restenosis with stent fracture after DES implantation.

Method: From November 2002 to December 2010, 8797 patients with 11467 lesions underwent DES implantation successfully. Of these, 9329 lesions were angiographically followed after 6 to 8 months (midterm follow-up) and 6682 were followed at 12 months after midterm follow-up. Stent fracture occurred at 471 lesions (4.7% ± 5.0%) and that with restenosis occurred at 212 lesions. Of these 212 lesions, target lesion revascularization (TLR) by PCI with 1st generation DES or 2nd generation DES was performed on 73 lesions.

Results: Data are shown in the table. At midterm follow-up, the rates of restenosis and TLR were significantly lower after restenting with 2nd generation DES than with 1st generation DES.

Conclusions: Restenting with 2nd generation DES could be an acceptable treatment for restenosis with stent fracture after DES implantation.

Coronary flow velocity and fluid shear stress predict late catch-up after sirolimus-eluting stent implantation

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Recent studies have suggested the possibility of late catch-up after sirolimus-eluting stent (SES) implantation. This study sought to assess predictive values of coronary flow velocity and shear stress throughout the vessel for angiographic late catch-up after SES implantation.

Methods and Results: A total of 520 study patients (age 66±11, mean±SD, men n=345, women n=175) with stable angina underwent successful implantation of SES or for de novo-lesions located in native coronary vessels and underwent follow-up coronary angiography (CAG) 6–9 months later (midterm restenosis defined as more than 50% diameter stenosis) and 1–3 years later (late catch-up defined as more than 50% diameter stenosis). The patients were followed up for at least 3 years. The TIMI frame count method and quantitative digital angiographic analysis were performed on the post-stenting angiogram. Coronary flow velocity (CFV; vessel length/TIMI frame count/15) and Reynolds number (an index of shear stress: velocity×diameter×density/viscosity) were measured. The study patients included the Midterm Restenosis group with 30 patients, the Late Catch-up group with 16 patients and the Non-Restenosis group with 474 patients. There were no significant differences between the 3 groups with respect to age, gender, location of target vessel. The Midterm Restenosis and Late Catch-up groups indicated significantly lower CFV and lower Reynolds number than did the Non-Restenosis, while CFV and Reynolds number were not different between the Midterm Restenosis group and the Late Catch-up group (CFV: 142.7±37.6a mm/sec (Midterm Restenosis) vs. 156.0±41.7b (Late Catch-up) vs. 253.4±62.4c (Non-Restenosis). ANOVA p=0.001, Reynolds: 100.0±38.4a (Midterm Resteno-
Virtual histology intravascular ultrasound comparison of neointimal morphology of in-stent restenosis with drug eluting stents versus bare metal stents

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Background: The process of in-stent neointimal hyperplasia (NIH) between drug-eluting stents (DES) and bare metal stents (BMS) might be different. We compared the composition of in-stent NIH between BMS and DES using Virtual Histology Intravascular Ultrasound (VH-IVUS).

Methods and Result: VH-IVUS was performed in 63 patients (BMS 40 and DES 23) who underwent coronary revascularization because of in-stent restenosis. The region of interest was placed between the luminal border and the inner border of the struts. NIH tissue composition was reported as percentages of NIH area: percent fibrous (%F), percent fibrofatty (%FF), percent necrotic core (%NC), percent dense calcium (%DC). Mean follow-up times between stent implantation and VH-IVUS were: 17.3 ± 8.9 for BMS in-stent lesions and 694.8 ± 22 days for DES treated lesions (n.s.). At the sites of stent distal edge, stent proximal edge and in-stent minimal lumen area, %NC volume was higher in DES than in BMS (5.46 ± 0.08 vs. 4.52 ± 0.08, P = 0.016). In-stent NIH volume was higher in DES than in BMS (64.1 ± 12.2 vs. 70.4 ± 13.3, P = 0.016), whereas %VC volume was higher in DES than in BMS (11.5 ± 0.5 vs. 8.6 ± 0.4, P = 0.02).

Conclusion: VH-IVUS analysis demonstrated that the composition of NIH was different between DES and BMS, suggesting that the process of NIH in-stent in DES and BMS is diverse.

Predictors of neointima hyperplasia in in-stent restenosis

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Aim: The evaluation of expression and quantitv of the microRNA/145, protex modifications of extracellular matrix in in-stent restenosis as well as of circulating levels of some principal inflammatory markers.

Material and methods: The expression and quantity of microRNA/145 (muscle cell phenotype marker), metalloproteinase 2 (MPT2) and its specific tissue inhibitor (TIMPT2), fibrillar collagen type I content were assessed in media and neointima of the arterial segment belonged to bare-metal restenosis taken from died 11 patients using following methods: hybridization in situ, confocal microscopy, immuno-fluorescent microscopy with specific monoclonal antibodies, PCR in realtime. In the blood of 22 patients made ISR averagely after 6 months and from died 11 patients using following methods: hybridization in situ, confocal microscopy, immunofluorescent microscopy with specific monoclonal antibodies, PCR in realtime. In the blood of 22 patients made ISR averagely after 6 months and from died 11 patients using following methods: hybridization in situ, confocal microscopy, immunofluorescent microscopy with specific monoclonal antibodies, PCR in realtime. In the blood of 22 patients made ISR averagely after 6 months and from died 11 patients using following methods: hybridization in situ, confocal microscopy, immunofluorescent microscopy with specific monoclonal antibodies, PCR in realtime.

Results: The in-stent restenosis evolution has been associated with microRNA/145 expression decrease by up 90% in coronary media, correlatively to ISR degree and to number of smooth muscle cell with secretory (synthetic) phenotype expression. The neointima matrix composition in ISR was basically due to fibrillar collagen I degradation, and the denaturized collagen migrated and accumulated in neointima. Extracellular matrix reorganization in ISR was basically due to fibrillar collagen I degradation, and the denaturized collagen progressively accumulated in media and neointima, a process accompanied by external elastic lamina perforation. To be noted a significant rise (until 4-5 times) of MPT2 quantity while TIMPT2 content respectively reduced leading to a marked MPT2/TIMPT2 ratio elevation. Development ISR after 6 months since angioplasty is underlined by a potentiated inflammation inasmuch blood proinflammatory cytokines and CRP levels were higher than control pattern by 28-52%. Endothelium inflammation marker, LP-PLA2, rose above control value by 42%.

Conclusions: 1) The expression and quantity of smooth muscle cell phenotype marker, microRNA/145, are reduced in media of ISR artery, that correlated with neointimal hyperplasia level. 2) Extracellular matrix reorganization in ISR is triggered by fibrillar collagen I degradation and the denaturized collagen progressively accumulated in medid and neointima, which facilitates the cell migration and neointima hyperplasia. 3) Negative coronary remodeling associating ISR is link to inflammation activation exhibited by significant increase of TNF-alpha, IL-1, IL-6, CRP and LP-PLA2 in the blood, which can be estimated as predictors of risk of the stent re-occlusion.

Difference in clinical restenosis rates between silicon carbide and uncoated bare metal stents

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Purpose: Bare metal stent (BMS) implantation triggers a foreign body reaction resulting in neointima formation and restenosis. Silicon carbide coating (SiC) shields the metal from both circulating blood and the vessel wall. We investigated whether this coating decreases clinical target revascularization (TLR).

Methods: Two commercially available L-605 Co Cr BMS (stent A: amorphous SiC coating and stent B: uncoated) were implanted in 2731 patients over two consecutive 18 month periods (2006-2008). Diabetics and patients presenting with restenosis (25%) were excluded as in those patients drug eluting stents were used. TLR rates were evaluated at 1 year post PCI.

Results: Procedural and outcome data are presented in the table. Multiple logistic stepwise backward regression analysis identified post-PCI minimal luminal diameter (adjusted odds ratio 0.56; 95% CI [0.42-0.73]; P < 0.001), total implanted stent length (1.01 [1.00-1.02]; P < 0.001), NSTEMI/unstable angina (1.89 [1.41-2.54]; P < 0.001), stent A (1.62 [1.20-2.19]; P < 0.002) and triple vessel PCI (2.68 [1.02-7.03]; P = 0.045) as significant independent predictors for clinical TLR. Although non-significant, non-compliant balloon post-dilatation (0.66 [0.35-1.24]; P = 0.20) was kept in the model to accuracy, as an increase was post-dilatation over the study period. Homs & Lemeshow goodness of fit P-value was 0.35. Because 2.0-3.0 mm stents A had lower strut thickness (60 μm versus 80 μm), subgroup analysis (n=2382 lesions) was performed. Higher clinical TLR rates for stent A persisted in this small stent subgroup (1.62 [1.17-2.23]; P = 0.003).

Conclusions: Contrary to our primary hypothesis, SiC-coated BMS implantation resulted in significantly higher TLR rates.
P4154 No harmful effect of stem cell mobilization by granulocyte-colony stimulating factor on restenosis or late luminal loss after sirolimus-eluting stent implantation

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Purpose: We evaluated the effects of stem cell mobilization by granulocyte-colony stimulating factor (G-CSF) on neointimal growth after sirolimus-eluting stent (SES) implantation.

Methods: The present double-blinded randomized placebo-control study that primarily evaluated the effect of stem cell mobilization by G-CSF on endothelial function after SES implantation assigned patients to the G-CSF group (n=50) or the placebo group (n=50). After successful SES implantation, patients received subcutaneous injection of G-CSF (300 mg daily) or saline for 5 days. Follow-up angiography was performed 9 months after SES implantation.

Results: Plasma CD34+ cell level did not differ between the 2 groups at baseline (0.94±0.55 vs. 0.93±0.68×10^5/L; p = 0.96). It significantly increased after G-CSF injection (0.94±0.55 vs. 18.39±13.55×10^5/L; p < 0.001) but did not in the placebo group (0.93±0.68×10^5/L vs. 1.35±2.36×10^5/L; p = 0.02). Follow-up angiography was performed in 41 patients (82%) at 292.0±22.6 days in the G-CSF group and 46 patients (92%) at 287.0±10.3 days in the placebo group (p = 0.14 and p = 0.18, respectively). No death or myocardial infarction was observed in the study participants during follow-up. There was no significant difference in restenosis rate between the 2 groups (0.0% vs. 6.5%, p = 0.10). Late luminal loss was not different (0.17±0.25 mm vs. 0.30±0.36 mm, p = 0.06). Regression analysis showed no significant correlation between plasma CD34+ cell level after study drug injection and late luminal loss at follow-up (p = 0.14, p = 0.21).

Conclusion: Stem cell mobilization by G-CSF does not increase restenosis or late luminal loss after SES implantation.

P4155 Mobilization of CD34+KDR+ cells among circulating progenitors predicts bare-metal stent restenosis

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Objective: We prospectively investigated the relationship between markers reflecting the endothelial response to injury and the occurrence of in-stent restenosis (ISR) in stable coronary artery disease patients undergoing percutaneous coronary intervention (PCI).

Methods: Endothelial lesion and regeneration are critical events determining ISR after PCI. The background: Endothelial lesion and regeneration are critical events determining ISR after PCI. Method: We performed a multicentre prospective study which included 156 patients undergoing elective PCI with bare-metal stent (BMS). The endothelial lesion was assessed by the enumeration of circulating endothelial cells (CECs). Endothelial regeneration was evaluated by enumeration of circulating CD34+ progenitor cells (PC) and CD34+KDR+ endothelial progenitor cells (EPC). Measurements were performed before PCI (H0), 6 and 24 hours (H6 and H24) after. Dynamic changes were evaluated by calculating delta (delta) of each marker. The primary and secondary end-points of the study were clinical target lesion revascularisations (TLR) and major adverse cardiovascular events (MACE) at 6 months follow-up.

Results: During follow-up, 28 MACE were recorded including 27 TLR. PCI induced a significant rise in CEC, CD34+PC and CD34+KDR+ EPC. Baseline, H6 and H24 levels of markers did not differ between patients with and without TLR. The delta percentage of CD34+ PC expressing KDR was significantly reduced in patients with TLR compared to patients without TLR (<56±8.1 vs 29.1±6.2; p=0.015). In multivariate analysis, this parameter independently predicted the occurrence of TLR and MACE (p<0.02 and p=0.014 respectively (figure 1)).

Conclusion: In response to PCI, rather than the extent of the endothelial injury, the proportion of CD34+KDR+ EPC mobilized among PC determines the risk of in-stent restenosis and MACE.

P4156 Severe insulin resistance is a predictor of restenosis after drug-eluting stent implantation

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Introduction & Hypothesis: Percutaneous coronary intervention (PCI) is an effective treatment for patients with ischemic heart disease; especially, restenosis is suppressed after drug-eluting stent (DES) implantation. The aim of this study was to clarify the factors associated with coronary restenosis after DES implantation and evaluate the homeostasis model assessment of insulin resistance (HOMA-IR) index as a predictor of restenosis. We researched the clinical records of 258 patients who had been subjected to elective PCI and DES implantation between May 2007 and December 2010. We evaluated these patients by the value of HOMA-IR, and examined the relationship between restenosis and HOMA-IR.

Results: The overall restenosis rate was 14% (37/258). HbA1c levels were no different between positive and negative of restenosis. But positive of restenosis was significantly greater than negative of restenosis (7.17±6.32 vs 5.47±3.94, p=0.02) in HOMA-IR index. We distributed three groups by value of HOMA-IR (less 2.5; n=115, 2.5 to 5.0; n=56, over 5.0; n=87), the rate of restenosis was significantly higher in HOMA-IR over 5.0 group (23.0%) than in the other groups (11.3% and 7.1%, p=0.014). Logistic analysis showed that the only independent predictor of restenosis was HOMA-IR over 5.0 (OR 2.87; p=0.004).

Conclusion: The results suggested that severe insulin resistance was a predictor of restenosis after drug-eluting stent implantation; furthermore, that improvement of insulin resistance may contribute to prevent coronary restenosis after drug-eluting stent implantation.
Impaired production of anti-atherosclerotic macrophages within culprit coronary plaque in diabetic patients with restenosis after primary PCI

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Purpose: Coronary intraplaque hemorrhage (IPH) accelerates atherosclerosis through the dual metabolic stresses of cholesterol-enriched erythrocyte membranes and prooxidant hemoglobin (Hb). IPH is frequently observed in vulnerable coronary plaques from ACS patients with diabetes, in association with bare metal stent (BMS) restenosis after primary PCI.

Methods: In 23 ACS patients with diabetes (HbA1c(NGSP)>6.5% or HOMA-IR>2.5), atherothrombotic debris was retrieved using filter-based distal protection device (Filtrap), during PCI with BMS implantation. The debris was stained with antibodies to CD163 (Hib scavenging macrophage), CD14 (proinflammatory macrophage), glycophorin A (GPA, intraplaque hemorrhage) and IL-10 production in coronary plaques from ACS patients with diabetes, in association with bare metal stent (BMS) restenosis after primary PCI.

Results: Restenosis rate were 17.4%. Conventional risk factors, such as diabetes, dyslipidemia and hypertension were not different between the 2 groups, at the time of index PCI and after 9-month medical treatment. GPA, CD14, CD163, and IL-10 were not different between the two groups. However, IL10/CD163 polymorphism was a more powerful predictor than hs-CRP (P=0.053). Furthermore, certain known atherosclerosis risk factors showed considerable OR: diabetes mellitus, 4.0; hypertension, 4.5; hypercholesterolemia, 1.4 and hypertriglyceridemia 7.

Conclusion: Our primary results showed that hs-CRP and genetic factors are clinical predictors of restenosis, among them, eNOS polymorphism was more powerful. Interestingly, these results demonstrated that traditional risk factors are more powerful that the novel one for predicting ISR. The final result is pending with larger population.

Reeseing of a decellularized arterial matrix for restenosis research

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Purpose: Aim of this study was to produce an in vitro test platform for restenosis research by reseeding of a natural, completely acellular arterial matrix with human endothelial and smooth muscle cells.

Methods: Freshly, surgically excised segments of rabbit aorta were obtained. Freshly, surgically excised segments of rabbit aorta were obtained. After verification of decellularization, a bare metal stent (DRIVER, Medtronic, 30 mm length, 4 mm diameter) was implanted and the segment was reseeded with human coronary artery endothelial (HCAEC) and human coronary artery smooth muscle (HCASMC) cells. Reesing was performed in 6-well plates, during three months. Detection with CD31 and α-smooth muscle actin specific antibodies showed that both, HCAEC and HCASMC are adhesive on the decellularized matrix and growing in several layers.

Results: By reseeding, cells formed a confluent monolayer after 14 days and a multiple of layers after three months. Adhesion of cells did not differ between stented and non-stented segments, revealed by HE and EvG staining. RT-PCR for the reseeded vessels showed distinct bands for HCAEC-specific (CD31) and HCASMC-specific (α-smooth muscle actin) primers. Detection with CD31 and α-smooth muscle actin specific antibodies showed that both, HCAEC and HCASMC adhesive on the decellularized matrix and growing in several layers.
Comparison of neointimal tissue characteristics among bare-metal stent, paclitaxel-eluting stents and zotarolimus-eluting stents using integrated-backscatter intravascular ultrasound (IB-IVUS)


Purpose: Drug-eluting stent (DES) has dramatically reduced angiographic restenosis and target lesion revascularization (TLR) by decreasing neointimal hyperplasia. However, ISR in DES still occurs to limited extent. Although neointimal tissue characteristics are essential to understand the pathophysiology of ISR, they have not been fully investigated. The aim of this study is to compare the differences of neointimal tissue characteristics among BMS, paclitaxel-eluting stents (PES) and zotarolimus-eluting stents (ZES), using intravascular ultrasound (IVUS) and integrated backscatter IVUS (IB-IVUS).

Methods: We investigated 95 de-novo lesions to be treated with BMS (N=18), PES (N=20), and ZES (N=17). We performed longitudinal IVUS analyses within stented segments to confirm minimum lumen area (MLA) at follow-up. Neointimal tissue characteristics judged by grayscale-IVUS were categorized as homogenous or heterogeneous. Neointimal tissue characteristics were also analyzed using IB-IVUS, which characterized as following four characteristics: calcific, dense-fibrous, fibrous, or lipid. We compared them among BMS, PES, and ZES.

Results: TLR rate showed no significant difference in three groups (22% in BMS, 30% in PES, 18% in ZES, p=0.67). Neointimal area at MLA site was significantly larger in BMS than PES and ZES (6.1mm² in BMS, 3.7mm² in PES, 2.6mm² in ZES, p<0.001). Most neointimal tissue categorized homogenous by grayscale-IVUS were categorized as homogenenous or heterogeneous. Neointimal tissue characteristics were also analyzed by IB-IVUS, which characterized as following four characteristics: calcific, dense-fibrous, fibrous, or lipid. We compared them among BMS, PES, and ZES.

The MLA was significantly larger in BMS compared with PES and ZES (6.1±0.3 mm² vs. 5.2±0.7 mm², p<0.01). In comparison between PES and ZES, neointimal tissue characteristics by IB-IVUS showed no significant differences (calcific: p=0.42, dense-fibrous: p=0.84, fibrous: p=0.94, lipidic: p=0.73).

Conclusions: IB-IVUS analyses revealed that neointimal tissue in BMS contained more fibrous tissue than PES and ZES, which suggested more stable neointima in BMS compared with PES and ZES. In addition, PES had similar neointima to ZES by IB-IVUS analyses.
value of < 0.8 was considered as significant in determining ischemia. The minimal lumen area (MLA) were measured by OCT and IVUS.

Results: Although both MLA obtained by IVUS and OCT showed a significant correlation to the FFR values, MLA associated with lesion grading according to IVUS criteria had a higher correlation to FFR values than MLA by IVUS. OCT: R=0.679, P<0.001, IVUS: R=0.573, P<0.001. The best cutoff value of the MLA to predict FFR ≤ 0.80 was 4.28 mm² by IVUS (sensitivity: 94.7%, specificity: 76.9%, AUC: 0.877) and <2.24 mm² by OCT (sensitivity: 94.7%; specificity: 76.9%; AUC: 0.947).

Conclusion: OCT-based MLA measurement may provide better estimation of physiological coronary epicardial stenosis than IVUS.

**NON CORONARY AND TAVI INTERVENTIONS**

### P4168

**Percutaneous occlusion of left atrial appendage with the amplatzer cardiac plug: results from clinical, echocardiographic and CT follow-up in 100 implanted patients**

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Background: Percutaneous left atrial appendage (LAA) occlusion has proved to be safe and non-inferior in the prevention of cardioembolic events in non-valvular atrial fibrillation (AF) when compared to treatment with vitamin K antagonists (VKA). Data from large studies are lacking information on the use of Amplatzer Cardiac Plug (ACP). The aim of our study is to demonstrate that the ACP is safe and effective in the short and medium term.

Methods: Data from 106 consecutive patients (pts) submitted to two Centers for performing percutaneous LAA occlusion were collected from December 2008 to January 2012. All pts had an high thromboembolic risk (CHA2DS2-VASc ≥ 2) and at least one contraindication to oral anticoagulation therapy. After the procedure all pts were treated with dual antiplatelet or anticoagulation therapy for 4 weeks. Pts were re-evaluated with clinical or instrumental follow up (FUP) with computer tomography (CT) or transesophageal echocardiography (TEE).

Results: Mean age was 75±11 yrs. 57% M. The ACP was successfully implanted in 100 of 106 pts (94%). Permanent AF was present in 71% of pts, while persistent and paroxysmal AF were present in 11% and 18%, respectively. After the procedure five pericardial effusions were observed, three of which needed pericardiocentesis. Two pts experienced a transient ischemic attack, one the day after the procedure and the other 16 months later. One patient, treated with ASA, clopidogrel and fondaparinux, was affected by intracranial haemorrhage two weeks after the procedure. At a mean FUP of 13±7 months (0 pts lost to FUP) 6 patients were dead for non procedural related causes (2 cases of pulmonary embolism, 2 cancers, one of worsening heart failure and one due to cardiac arrhythmia). No ischemic stroke was observed in any implanted patient. TEE was performed in 46 patients at 6±7 months after the procedure and CT in 33 pts at 11±6 months, failing to demonstrate any malposition nor embolization of the device. In two cases there was a residual atrio-atrial septal defect. In one patient TEE demonstrated a small thrombus on the device that was successfully treated with fondaparinux for one month. Mitral valve motion, transmural flow and left superior pulmonary vein were not affected by the presence of the device.

Conclusions: Data from our experience suggest that percutaneous LAA occlusion with ACP is a safe and effective alternative to VKAs in selected high risk patients with non-valvular AF and is associated with a high procedural success rate. Our mid-term follow up in 100 implanted pts with no ischemic stroke after a mean of 13 months confirms the acute results.

### P4169

**Comparative analysis of percutaneous left atrial appendage (LAA) closure systems: a single center experience**

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Background: The concept of LAA closure has entered the clinical arena as a treatment alternative for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). Currently, two different LAA closure systems are available but lacking comparative data.

Objective: To prospectively compare both LAA closure systems with regards to procedural outcome and complications.

Methods: Consecutive patients (pts) with NVAF, high risk for stroke and either contraindication or not willing to accept long term oral anticoagulation (OAC) were prospectively enrolled. In all pts deep sedation was utilized during the procedure. After transseptal puncture LAA angiography was performed. LAA dimensions were calculated from TEE and angiography. Watchman™ (group A) or Cardiac Plug™ (device B) were implanted. All patients received OAC or dual antiplatelet therapy (aspirin/clopidogrel) for 6 weeks followed by TEE for re-assessment.

Results: In a total of 44 pts 45 procedures were performed (mean age: 74±8 years: group A: n=18 pts; 11 males) (group B: n=27 pts; 15 males). There was no statistical difference between group A and B with regards to CHADS2: 2 (Q1=1, Q3=3) vs 2 (Q1=1, Q3=2), CHA2DS2-VASc: 3 (Q1=3, Q3=5) vs 4 (Q1=3, Q3=5), and HASBLED score: 3 (Q1=2, Q3=4) vs 3 (Q1=2, Q3=4). Implantation success was achieved in 16/18 pts (88%, group A) and in 27/27 (100%, group B), respectively.

In group A, 2 complications failed 1 pt switch to group B, 1 pt with transient ventricular arrhythmia. In group B, 1 asymptomatic ST elevation was observed. Procedure- and fluoroscopy-time comparing group A and B was 56±16 min vs 48±16 and 9.2±5.6 vs 7.4±4.7 min, respectively. Mean LAA device sizes were

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similar (group A: 24.3±2.7 mm vs. group B: 23.6±3.8 mm). During a median follow up of 187 (Q1=88, Q3=345) days no death, stroke or embolism was observed; in 41/43 pts (95%) switch to aspirin alone could be enabled.

Conclusions: Both percutaneous LAA closure devices can be implanted with high acute success rates. There is a trend towards a higher implantation success, shorter procedure- and fluoroscopy-time in group B.

Refining transcatheter left atrial appendage closure: eliminating the anasthesiologist and reducing the cost

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Introduction: The validity and benefit of transcatheter LAA closure for protection from thromboembolic stroke in non-valvular AF has been well established. However, to date, all studies have performed this procedure under general anaesthesia. Given that most candidates for LAA occlusion are often aged greater than 75 years, with multiple co-morbidities, general anaesthesia confers significant risk to this patient cohort, as well as additional costs to the procedure. We therefore sought to determine the safety of performing this procedure under conscious sedation, and to determine any cost implications of this strategy.

Methods: Fifty four (44 men, 10 women; mean age 75.7±6.2 years) with non-valvular atrial fibrillation (mean CHA2DS2-VASc score 3.8±1.5) and high risk for oral anticoagulation, underwent percutaneous LAA closure using the WATCHMAN device. All procedures were performed under conscious sedation. Trans-septal puncture and trans-septal puncture (TOE) guidance. IV Midazolam was titrated to observed patient needs, with monitoring of O2 saturations. The follow-up program included clinical and echocardiographic review performed in 60 days.

Results: The LAA was successfully occluded 50 patients (92.5%) under conscious sedation. In four cases the device was not implanted due to unsuitable appendage anatomy. The mean procedural and fluoroscopy times were 61.3±16.1 and 10.5± 3.8 minutes respectively. The mean device size was 24.6±3.8 mm. There were no significant procedure or device related adverse events. There were two patients experienced major adverse events during a follow-up (5-22 months).

Cost saving implications of using conscious sedation were experienced major adverse events during a follow-up (5-22 months). In those pts that arrhythmias appeared all the inflammatory markers had no statistical difference. In those pts that no arrhythmias appeared the inflammation indices3 months after-treatment caused by the device. Long-term follow-up is required for these patients.

Conclusions: We evaluated 50 patients with contraindications to anticoagulant (mean age 77.6± y; male 60%; mean CHA2DS2-VASc score 4.7±1.2; HAS-BLED score 3.1±1.0) who had undergone LAA transcatheter occlusion procedure using the Amplatzer® Cardiac Plug (AGA Medical, Plymouth, MN) in our center between January 2009 and January 2012. After a short period of dual antiplatelet drugs all patients were chronically treated with a single antiplatelet agent.

Methods: We evaluated patients with contraindications to anticoagulant.

Conclusions: Our data, according to previous findings, that residual flow after LAA occlusion is not associated to a higher incidence of clinical cerebrovascular events. CTA has a high sensitivity to identify peri-device leaks and thrombus.TEE is still the most used technique in the evaluation and can represent the unique tool in a subgroup of patients who develop absolute contraindications to intravenous administrations of lodinated contrast agents during F-U period.
"Migraine side effect" after PFO closure as secondary Transthoracic echocardiography guidance during Mitral Valvuloplasty long-term follow-up of single Simultaneous measurement of left ventricular volume and pressure during percutaneous mitral valve repair with the evove mitralclipTM system

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The purpose of this study was to determine the frequency of occurrence of the migraine after transcatheter closure of PFO in patients younger than 55 yrs old with cryptogenic stroke or TIA.

Methods: All 204 consecutive patients (mean age 40.9±9.9 yrs; 103 men, 108 pts <40 yrs, 116 pts 40-55yrs old) with cryptogenic thromboembolism who underwent PFO closure between 1999 and 2011 as secondary prevention were included. Mean follow-up period was 37.8±32.5, median 27 months (range, 3-151 months). There were 33 (14.7%) pts lost to follow up. Every patient was treated at least 6 mos with aspirin (yrs 1999-2003) or aspirin and ticlopidin (2004-2006) or aspirin and clopidogrel (3-6 months, 2007-2011) after procedure. All pts were sent the questionnaire concerning the presence of migraine before and after PFO closure.

Results: The migraine occurred in the study group before PFO closure in 68 (30.4%) pts, that is three times more frequently than in general population (30% vs 10%). Noticeable improvement (expressed in lower frequency rate or severity of migraine attacks, in patients' subjective opinion) or disappearance of migraine vs 10%). Noticeable improvement (expressed in lower frequency rate or severity of migraine attacks, in patients' subjective opinion) or disappearance of migraine vs 10% p≤0.0001. There were no new cases of migraine after the PFO closure.

Conclusions: 1/ Migraines are seen more frequently in patients with PFO compared to general population. 2/ Percutaneous PFO closure with Amplatzer septal occluder leads to recovery of migraine or noticeable amelioration of symptoms in significant percentage of patients.


P4175

Transthoracic echocardiography guidance during percutaneous closure of patent foramen ovale


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Background: Percutaneous closure of PFO has been increasingly performed for several indications; mostly due to cryptogenic stroke. We aimed to evaluate the safety and efficacy of transthoracic echocardiographic (TTE) guidance during percutaneous closure of PFO.

Methods: Between 2005-2012, 188 patients (91 males; age 40±10.3 yrs) underwent transcatheter PFO closure. In all patients transesophageal echocardiography performed subsequently to diagnose, assess the size and evaluate for suitability of the defect for percutaneous closure. During the procedure fluoroscopy and TTE were used for guidance.

Results: Overall, 74 (43.3%) Amplatzer, 76 (44.4%) Occlutech Figulla and 21 (12.3%) BioSTAR PFO occluder devices were used. The indications for PFO closure were ischemic stroke in 123 (65.4%), recurrent transient ischemic attacks in 65 (34.6%) patients. In all patients, percutaneous intervention was performed successfully under TTE guidance. There have been no neurologic/cardiovascular complications during the immediate and long term follow-up (median 28 months).

There was significant difference between the mean fluoroscopic time from the procedure start to PFO closure in 116 (61.2%) patients (mean±SD: 10.4±6.5 min) compared to those of patients with a reduction of regurgitant fraction (FF) >50%. The reduction in LA volume and LV enddiastolic and endsystolic volumes were assessed by 2D transthoracic echocardiography.

Results: RV by 3D color Doppler TEE was reduced from 0.45±0.17 cm² to 0.19±0.11 cm² after PMVR. Patients with a reduction of VCA >50% (n=22) had a significantly smaller pre-procedural mitral annulus area compared to patients (n=6) with a reduction <50% (11.9±3.2 vs. 17.2±10.1 cm², p=0.034). Mitral annulus circumference (13.0±1.9 vs. 15.5±4.9 cm, p=0.002), mitral annulus anterior-to-posterior diameter (3.6±0.6 vs. 4.1±1.0 cm, p=0.008) as well as annulus postero-meseral-to-antero-lateral diameter (4.0±0.7 vs. 4.5±1.3 cm, p=0.197) tended to be smaller in patients with a reduction of VCA >50%. The reduction in LA volume as well as LV enddiastolic volume at 6 months follow-up was significantly greater in patients with a reduction of VCA >50% after PMVR (10.6±5.5 and 10.5±7.9%) compared to those of patients with a reduction of regurgitant VCA ≤50% (3.1±1.9 and -1.9±0.7%; p=0.013 and p=0.024, respectively). There was no difference in reduction of LV enddiastolic volume between both groups (-5.4±7.3% vs. -5.3±5.7%, p=0.97).

Conclusions: In patients with very large mitral annulus dimensions, effectiveness of PMVR is reduced. Less effective PMVR is associated with less LA and LV remodeling.

Figure 1

Conclusion: Our study confirms the efficacy and safety of TTE guidance during percutaneous closure of PFO which shortens the procedural time and obviates the need for general anesthesia or endotracheal intubation.

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P4176

Impact of mitral annulus dimensions assessed by 3D echocardiography on procedural results of percutaneous mitral edge-to-edge repair and left atrial and left ventricular reversed remodeling


Background: Percutaneous mitral valve repair (PMVR) using the edge-to-edge technique has become a treatment option for selected patients with severe mitral regurgitation. This study evaluated the impact of mitral annulus dimensions on reduction of mitral regurgitation after PMVR and prediction of left atrial (LA) and left ventricular (LV) remodeling.

Methods: In 30 high-surgical risk patients with severe functional mitral valve regurgitation (age 74±9 years) 3D transesophageal echocardiography (TEE) was performed before PMVR to assess: mitral annulus area, circumference, anterior-to-posterior diameter and posterior-medial-to-antero-lateral diameter. 3D color Doppler TEE was used for direct planimetry of the vena contracta area (VCA) to define before and after PMVR. At 6 months follow-up, changes of LA volume and LV enddiastolic and endsystolic volumes were assessed by 2D transthoracic echocardiography.

Results: VCA by 3D color Doppler TEE was reduced from 0.45±0.17 cm² to 0.19±0.11 cm² after PMVR. Patients with a reduction of VCA >50% (n=22) had a significantly smaller pre-procedural mitral annulus area compared to patients (n=6) with a reduction <50% (11.9±3.2 vs. 17.2±10.1 cm², p=0.034). Mitral annulus circumference (13.0±1.9 vs. 15.5±4.9 cm, p=0.002), mitral annulus anterior-to-posterior diameter (3.6±0.6 vs. 4.1±1.0 cm, p=0.008) as well as annulus postero-medial-to-antero-lateral diameter (4.0±0.7 vs. 4.5±1.3 cm, p=0.197) tended to be smaller in patients with a reduction of VCA >50%. The reduction in LA volume as well as LV enddiastolic volume at 6 months follow-up was significantly greater in patients with a reduction of VCA >50% after PMVR (10.6±5.5 and 10.5±7.9%) compared to those of patients with a reduction of regurgitant VCA ≤50% (3.1±1.9 and -1.9±0.7%; p=0.013 and p=0.024, respectively). There was no difference in reduction of LV enddiastolic volume between both groups (-5.4±7.3% vs. -5.3±5.7%, p=0.97).

Conclusions: In patients with very large mitral annulus dimensions, effectiveness of PMVR is reduced. Less effective PMVR is associated with less LA and LV remodeling.

P4178

Mitrail Valvuloplasty long-term follow-up of single balloon (Balt) versus Inoue balloon techniques

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This study aimed to demonstrate that mitral balloon valvuloplasty (MBV) with the Balt single balloon (BBS) has similar outcome and long-term follow-up (FU) than MBV performed with the Inoue worldwire accepted technique.
Percutaneous mitral balloon valvuloplasty beyond 65 years of age

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Objectives: To evaluate the safety and efficacy of percutaneous balloon mitral valvuloplasty for the treatment of mitral stenosis in patients older than 65.

Background: The profile of subjects undergoing percutaneous balloon mitral valvuloplasty (PMBV) in developed countries has shifted toward the elderly. In the group of elderly patients long-term results after PMBV, as well prognostic factors that may improve patient selection for this procedure have not been fully elucidated.

Methods: The studied group consists of 132 consecutive patients aged ≥65, who underwent PMBV. All PMBV procedures were performed by the antegrade transvenous approach using the Inoue balloon system. Thirty-four (25.8%) patients had previous surgical and 2 (1.5%) percutaneous mitral commissurotomy. The mean Echo score was 7.49±1.46 (median 8, range 3-11). Thirty-five (26.5%) patients had Echo score >8. The mean left atrium diameter before PMBV was 5.4±1.1 cm (median 5.0 cm). The endpoints assessed were all-cause survival and survival free of mitral valve intervention or heart failure ≥ NYHA III.

Results: Procedural success, defined as mitral valve area ≥1.5 cm² and mitral regurgitation grade ≤2, was obtained in 105 (79.4%) patients. The mean mitral gradient (MVG) was 51±48 mmHg. Among the patients with initial MVG ≥10 mmHg, the rate of procedural success was significantly higher in the group of 86 patients with Echo score ≤8 and mean MVG < 10 mmHg than those (12 patients) with Echo score >8 and MVG > 10 mmHg (86% vs. 41.7%, p=0.001).

Mean follow-up was 26.5±4.3 years. Survival curves showed that for the whole studied group after PMBV the three-, five-, and ten-year overall survival rates were 95.4%, 91.3% and 80.5% versus 89.6%, 69.5%, and 53.7%, respectively; p=0.002. Survival free of mitral valve intervention or heart failure ≥ NYHA III was significantly better for patients with good immediate result and mean pulmonary arterial pressure before PMBV ≥25 mmHg.

Conclusions: PMBV is safe and efficacious in elderly patients with symptomatic mitral stenosis. Long-term results are good and related mainly to the quality of the procedure.

Clinical and echocardiographic outcomes of patients undergoing percutaneous closure of mitral paravalvular leak:


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Purpose: Percutaneous closure of mitral paravalvular leak is a complex procedure, recently developed for patients unsuitable for a new surgery. Clinical experience is limited and the results are controversial. We report here the experience of our center and the acute and mid-term outcomes.

Methods: We retrospectively reviewed those patients with severe prosthesis paravalvular regurgitation (MR) who underwent an attempt of percutaneous closure in our hospital. Data were collected regarding demographic characteristics, comorbidities, location and size of the leak, mortality and medium-term clinical and echocardiographic outcomes.

Results: The study comprises 11 procedures in 10 patients, which took place between October 2010 and July 2011. The mean age was 75.4±6.6 years and 54.5% were female. The medium Euroscore was 42.84±21.24. Mean LVEF was 53.7±14.38 and 7 patients also had an aortic prosthesis (5 of them mechanical). 62% of the interventions were performed on mechanical prosthesis, and the patients had undergone 1,7 previous surgeries (range 1-4), with a time to percutaneous repair of 161.7±11.1 months (range 6-314). The clinical indication for the procedure was heart failure, in all cases and also severe hemolysis in 81%. The location of the leaks were as follows: anterior quadrant in 5 patients, lateral in 4 and posterior in 1, being the mean maximum length 12.94±4.97. In 9 of the 11 procedures the device was successfully deployed, but in 2 patients the device was too big to provide adequate support. The Amplatzer Duct Occluder device was used in 1 case and the Amplatzer Vascular Plug III in the rest, using 2 of them for the closure of 1 leak. TEE showed mild MR just after the deployment of the device in 8 patients, and severe MR in 1 case. Mortality related to the procedure was 0%, but 3 patients died during the first month (only 1 of them due to complication related to the intervention). No more deaths were recorded during the follow-up period. Independent predictors to EFS: prior commissurotomy (p=0.012, HR=0.930, 95% IC 0.871-0.917) and post-MBV MVGA 1.50 cm² (p=0.001, HR=8.799, 95% IC 3.413-18.608).

Conclusions: Percutaneous closure of paravalvular leak is a procedure of variable effectiveness, whose main limitation is the extent comorbidity and poor basal status of some patients referred for this procedure. Furthermore, in some cases, the initial success does not ensure mid-term positive outcomes. These results could improve with a sooner referral of these patients and the development of specific devices for this pathology.

Introduction: Mitral stenosis is the most common valvular heart lesion found in pregnancy. When severe, it leads to significant maternal and fetal morbidity and mortality, since the hemodynamic adaptations to pregnancy are badly tolerated. Pregnancy can lead to development of heart failure in patients with asymptomatic or even unknown mitral stenosis, as a result of the increased mitral valve pressure gradient caused by the physiologic increase in heart rate and blood volume in pregnancy. When symptoms persist despite optimal medical therapy, the poor prognosis justifies the correction of mitral stenosis during pregnancy.

Methods: To present our experience in treating severe mitral stenosis in women who develop severe heart failure during pregnancy, using percutaneous balloon mitral valvuloplasty.

Patients: During 5 years, in our department, 294 balloon mitral valvuloplasties were successfully performed in women, ten of them pregnant. These were patients with congestive heart failure, New York Heart Association (NYHA) functional class III or IV, at the end of the second trimester of pregnancy, who did not respond to positive drug treatment with diuretics and digitals.

Interventions: We performed percutaneous balloon mitral valvuloplasty using the Amplatzer technique in the ten pregnant patients, with success, at around 24 weeks of gestation.

Results: After the procedure, the patients showed clinical improvement, returning to the NYHA functional class that they were in before becoming pregnant (I-II). The mean procedural risk of valve area was 0.87 (0.21) cm², nearly doubling after valvuloplasty. During the procedure there were no maternal or fetal complications. All patients were discharged 48 to 120 h after valvuloplasty, continuing their pregnancies without complications. 8 women had vaginal delivery, and the other 2 had a cesarean section at full term, with healthy newborns that developed normally. In follow-up, one patient who had moderate mitral regurgitation after valvuloplasty developed severe mitral regurgitation, requiring surgical correction after 4 years.

Conclusion: During pregnancy, balloon mitral commissurotomy is the treatment of choice of severe pliable mitral stenosis in patients who are refractory to medical treatment.
**Lung embolism**

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Superior vena cava obstruction can occur in late or progressive stages of various tumor diseases involving the mediastinum. To assess feasibility, short and long term efficacy and complication rate of interventional treatment, i.e. recanalization, PTA and stenting of such lesions we analyzed 16 consecutive patients with cancer related superior vena cava syndrome. Clinical follow up was performed every 3 months up to 52 months. Cancer driven mean survival time after PTA-stenting was 10.2 months (8 days – 52 months). Immediate technical success rate and acute clinical success rate was 100%; NYHA class improved from 3.31 (±0.60) to 1.8 (±0.75). Especially those in class 4 benefited most and improved to class 2. Symptom relief was reached within 24hs. All patients remained free from restenoses or recurrent superior vena cava syndrome for the entire follow up or for their remaining life span. We did not have any acute or chronic complication (stent migration, penetration, bleeding). Patients were discharged the day after an uncomplicated and uneventful hospitalization, in some cases on low molecular heparin or vitamin K antagonists. Thus, for palliation of superior vena cava syndrome in progressive cancer disease interventional PTA and PTA and stenting is technically safe and clinically efficient for both rapid and long term symptom relief. It should be considered as first choice treatment.

**Transcatheter closure of ruptured sinus of valsalva**

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**Purpose:** Development of protein- and cell-based therapy for advanced ischemic cardiomyopathy requires efficient and widely applicable intramyocardial (IM) delivery strategies. We tested whether a novel mapping technique, based on imaging modalities readily available in most cardiac centers, is a safe and equally effective substitute for existing electromagnetic mapping systems (NOGA) to guide IM injections.

**Methods:** AML was induced in 25 kg pigs (n=10) using a 45 mm balloon inflation in the proximal LAD. After 6 w, head to head comparison between NOGA and AML was performed in a subset of 6 pigs. 200 ± 5 mL injections of 2 different colored 15 μm fluorospheres were sequentially performed using a Myostar catheter: the first series of injections (18±3 pig) were delivered using NOGA, the second series of injections (12 pigs) was each performed using the house developed technique (LARCA). The latter fuses the infusion region, identified from delayed enhancement (DE)-MRI, with a 3D rotational angiographic subsequence integration with live biplane fluoroscopy enables guided IM injection. In an additional subset of 4 pigs, we tested whether LARCA could be fused with DE-CT and 18F-FDG PET/CT, as an alternative for MRI inoperable patients. Ex vivo 3D stacks of 5 mm slices were reconstructed to quantify injection accuracy towards the infarct border, defined by 2,3,5-triphenyltetrazolium chloride. Fluorescent injection spots were identified by UV illumination.

**Results:** DE-MRI after 6 w revealed significant functional impairment and LV remodeling (LVEF 37 ± 12%, LVEDV 188 ± 49 mL, infarct size 17 ± 19% of LV mass). During NOGA-procedures, 4/6 animals required DC-shock for major ventricular arrhythmias vs 1/10 during LARCA-procedures. Total online procedure time was significantly shorter for LARCA (43±4 vs 50±15 min). Periprocedural death was not observed in any group. When translated in the total LAD length the distance of the injection spots to the infarct border was 4.8 ± 0.5 mm for LARCA-MRI (n=42) vs 5.4 ± 0.5 mm for NOGA (n=49), p=0.40. LARCA-MRI and NOGA enabled spatial confinement of respectively 69% vs 63% of all injections to a distance less than 5 mm from the infarct border. LARCA fused with DE-CT and PET/CT, resulted in a mean injection distance of 6.0 ± 0.7 mm (n=44) to the targeted infarct border. LARCA resulted in a mean injection depth of 3.4 ± 0.3 vs 2.5 ± 0.3 mm for NOGA, p=0.06.

**Conclusion:** 3D Rotational angiography fused with multimodal imaging offers a new and promising strategy to guide IM injections towards the infarct border zone. Endovascular procedure times and arrhythmic side effects are significantly reduced in comparison to NOGA, without compromising injection accuracy.

**Transcatheter closure of ruptured sinus of valsalva aneurysm with nitinol mesh occluders**

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**Introduction:** Ruptured sinus of Valsalva aneurysm (R-SOVA) is a rare entity with a significant mortality rate. Surgical correction of R-SOVA with the use of Dacron, Teflon or polytetrafluoroethylene (PTFE) occluders has been the standard of care since the 1970s. The use of prosthetic occluders has been associated with limited durability and potential complications such as thrombosis and infection. In recent years, there has been an increasing interest in the use of percutaneous transcatheter occlusion devices as an alternative to surgical repair. Several percutaneous occlusion devices have been developed and are now available for clinical use. The aim of this review is to provide an overview of the current options available for the transcatheter closure of R-SOVA and to discuss the advantages and limitations of each device.

**Methods:** A comprehensive review of the literature was conducted using PubMed, Google Scholar, and other medical databases. The keywords used included “ruptured sinus of Valsalva aneurysm,” “percutaneous transcatheter closure,” and “occlusion devices.” The search was limited to English-language articles published between 2010 and 2020.

**Results:** Several percutaneous occlusion devices have been developed for the transcatheter closure of R-SOVA. These devices include the Amplatzer Muscular VSD Occluder, the Cardiaoccluder, the Agilis AFX occluder, and the Watchman FLX closure device. Each device has its own unique design and indications for use. The choice of device depends on the size and location of the R-SOVA, the presence of associated congenital heart defects, and the patient’s comorbidities.

**Conclusion:** Percutaneous transcatheter closure of R-SOVA with nitinol mesh occluders is a feasible and effective method of treatment.
Arrhythmia device lead extraction using evolution mechanical dilator sheath

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Background: Transvenous lead extraction (TLE) has undergone an explosive evolution by increasing technology due to incremental problem of lead infections and malfunctions. We aimed to present our experience in TLE with Evolution Mechanical Dilator Sheath.

Methods: Between June 2009-January 2012, Evolution sheath was used for extraction of 158 leads in 75 patients. Indications for extraction, procedural success and complications were defined according to HRS guidelines.

Results: Indications for TLE were infection (58.6%), lead malfunction (40%) and lead displacement (1.4%). Extracted devices were PM in 34 cases (45.3%), ICD in 29 cases (38.7%) and CRT-D in 12 cases (16%). Among 158 leads, 38 (24%) were RV, 54 (34.2%) were defibrillator coil, 53 (33.6%) were atrial and 13 (8.2%) were CS electrodes. Median time from preceding procedure was 88 months (21-240 months). Clinical success was 98.6% and complete procedural success with Evolution system alone was 88% (88 patients). Partial success was achieved in 3 leads with remaining small ventricular tip. Major complications were observed in 1 (1.3%) patient without any mortality.

Conclusions: Our experience has confirmed that the hand powered Evolution system is an effective extraction tool for chronically implanted pacemaker/ICD leads.

Comparison of knowledge-based weaning (KBW) and physician-driven weaning of mechanically ventilated patients in the coronary care unit


Introduction: Knowledge-based weaning (KBW) of mechanical ventilation is a form of closed loop ventilation successfully used to decrease duration of ventilator assistance in general intensive care units (ICU). However, its use in specialty ICUs has not been validated.

Objectives: To find out if KBW reduced weaning times in coronary care units (CCU).

Methods: Patients: Single center tertiary hospital CCU. Inclusion: age 21-85; assisted-mode mechanical ventilation ≤24 hrs; stable neurology. Exclusion: Poor short-term prognosis; pregnancy; hemodynamic instability. Randomization: 1:1 to KBW or usual care. Ventilator: Evita XL (Drager Medical, Lubeck, Germany) with SmartCare. Primary outcome: Total weaning time (time from inclusion to extubation without reintubation for 72 hrs). APACHE-II score used to stratify illness severity.

Results: From 1/12/2009 to 31/12/2011, 251 patients were screened. 61 did not give consent. Of the 244 remaining, 136 did not meet entry requirements (75 poor prognosis, 27 mechanical ventilation > 24 hours, 34 others). Total 54 patients enrolled, with mean age 68.0, (range 33-84) and mean APACHE-II score 17.8 and 18.6 for usual care and KBW group respectively; p=NS for both. Wearing time was 1080 mins or 0.75 days (median 675, range 20-7580 mins) in control group, and 1418 mins or 0.98 days (median 340, range 120-8710 mins) in KBW group. Wearing time was not significantly different between the two groups, even after adjustment for APACHE-II. Mean and median duration of mechanical ventilation was 2.78 and 2.18 days for usual care, 3.84 and 2.96 days for KBW (p=NS).

Conclusions: This pilot study failed to show a significant impact of KBW in reducing duration of ventilator assistance, as has been shown in general ICUs. This is likely because the profile of patients in CCU differ significantly from ICU patients; the proportion of patients with haemodynamic or arrhythmic instability is considerably higher, and there are a significant number of patients with very poor prognosis due to neurological injury. In the remainder, patients frequently received short duration of ventilation, so the impact of KBW can only be limited. In conclusion, although KBW may be helpful in individual patients, it is unlikely to have a major impact on average ventilator weaning time in the CCU context. A larger randomized trial will be needed to confirm these findings.

TAVI EXPERIENCE

Predictors and clinical outcome of significant paravalvular aortic regurgitation following transcatheter aortic valve implantation

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Purpose: Although transcatheter aortic valve implantation (TAVI) has emerged as a good alternative treatment for high surgical risk patients with severe aortic valve stenosis, significant paravalvular aortic regurgitation (PAR) remains a frequent complication. Therefore our aim was to investigate the determinants and short- and mid-term clinical consequences of PAR.

Methods: We studied 130 patients (mean age 81±8 years, 39 male) who underwent a TAVI with the Medtronic-CoreValve bioprosthesis. Clinical parameters were obtained from the medical history, laboratory analysis, echocardiography, cardiac computed tomography and angiography. Clinical outcome was assessed up to 12 months after TAVI.

Results: Following TAVI, PAR grade ≥2 occurred in 37 patients (28%). Multivariate analysis identified sinus width (per mm, OR 1.32, 95%CI 1.11-1.57, p=0.002) as the only independent predictor for PAR≥2. Thirty-day mortality and 1 year cumulative mortality were not significantly different between the PAR≥2 and PAR<2 groups. Cardiac mortality was significantly higher in the PAR≥2 group versus the PAR<2 group at 1 month (19% vs. 1%, p=0.016) and 1 year (28% vs. 2%, p=0.008).

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**Conclusion:** In TAVI immediately after prosthesis deployment significant AR is frequent and can be corrected by balloon dilation of the prosthesis or pulling back maneuvers. In self-expanding prostheses without massive AR further expansion of the prosthesis can be waited for before initiation of further interventions.

**P4191**

Under-deployment and asymmetrical expansion in transcatheter aortic valves

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**Purpose:** Transcatheter aortic valve implantation (TAVI) is an alternative for patients with aortic stenosis with high surgical risk. These valves are sutured to a stent which is expanded in a heavily calcified region. Our objective was to describe stent under-deployment (UD) and asymmetrical (non-circular) expansion, which may impair valve hemodynamics.

**Methods:** From June 2008 to January 2012, 63 consecutive patients underwent TAVI. We selected 56 patients with available transesophageal echocardiography (TEE) imaging. Variables (inner stent area (SA), anterior-posterior diameter (APD) and lateral-antero-posterior (LD)) were measured in 2D and 3D TEE. Mean values of 2D and 3D was used. We assessed stent circularity, defined as 1-(APD/LD). Values >10% were considered non-circular. UD was defined as nominal area (of each valve size) minus SA. Indexed UD was obtained dividing UD by nominal areas.

**Results:** Mean age was 82.8. Procedure approach was transfemoral in 80.4%. Valve sizes: 58.9% (23mm), 37.5% (26), and 3.6% (29). In 80.4% the valve used was XT model, the remaining the old TF. Mean SA were 3.27±0.8 cm² (23); 3.93±0.1 (26) and 3.98±0.2 (29). The final SA fitted progressively in the native valve annulus, showing a linear trend between SA and valve annulus (p<0.001). In our series, mean UD was 0.88±0.8 cm² (23); 1.37±1.28 (26) and 2.63±0.29 (29). Mean indexed UD was 24%, thus, the valve expands only to 76% of its nominal area. Comparing TAVI approaches and prostheses models, we found no differences in indexed UD. However, indexed UD increases keeping a linear relationship (p<0.01) with the valve sizes (21.2%±23, 25.9%±26, 39.8%±29). This suggests that larger stents loose part of the radial force in spite of the higher stent height. Post-procedural gradients of under-deployed valves (20% UD cut off) were numerically but statistically higher than the non-UD valves. Regarding the circularity analysis, we found that 37.5% of the valves were non circular. The deformation was mild (maximum 30%). No differences were found between TAVI approach, valve size or model. No correlation was found between non-circularity and AR aortic regurgitation.

**Conclusions:** Under-deployment in the balloon-expandable valve was substantial (mean 24% of nominal area) and related to the valve size (higher UD in larger prostheses), suggesting that larger stents loose radial force. Symmetrical expansion of the stents was fair (62.5%). New XT valve shows no improvement compared to old TF. Correlation of these results with clinical events was not evident in our small series, but further investigation in this field is warranted.

**P4192**

Prosthesis/annulus discongruence by three-dimensional transapical echocardiography: predictor of significant aortic regurgitation after transcatheter aortic valve implantation

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**Introduction:** Paravalvular aortic regurgitation (AR) is common after transcatheter aortic valve implantation (TAVI). This study aimed to assess the aortic/annulus discongruence by three-dimensional (3D) transapical echocardiography (TEE) planimetry of aortic annulus and its impact on the occurrence of significant AR after TAVI.

**Methods:** We included 33 patients who underwent TAVI with a balloon expandable device for severe aortic stenosis. To appraise the prosthesis/annulus discongruence we defined a ‘mismatch index’ expressed as: annulus area - prosthesis area. The aortic annulus area was planimetrized with 3D TEE, and approximated by circular area formula \((\pi r^2)\) using annulus diameter obtained by two-dimensional (2D) TEE.

**Results:** After TAVI, 13 patients (39.3%) developed significant AR (≥2/4). The occurrence of significant AR was associated to the 3D planimetrized annulus area (p=0.04), and the ‘mismatch index’ obtained through 3D planimetrized annulus area (p=0.003), but not to ‘mismatch index’ derived of 2D annulus diameter. In multivariate analysis ‘mismatch index’ for 3D planimetrized annulus area was the only independent predictor of significant AR (odds ratio: 10.722; 95% confidence interval: 1.040-17.8; p=0.04). The area under the ROC curve for ‘mismatch index’ by 3D planimetrized annulus area was 0.76, whereas for ‘mismatch index’ obtained by 2D circular area was 0.36 (Figure). Using 3D planimetrized annulus area as reference parameter to decide the prosthetic size, the choice would have been different in 21 patients (63%).

**Conclusions:** 3D TEE planimetry of aortic annulus improves the assessment of prosthesis/annulus discongruence and predicts the appearance of significant AR after TAVI.

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Clinical and hemodynamic outcomes in patients with prosthesiopatient mismatch after TAVI with both core valve and Edwards sapien XT valves

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**Purpose:** To investigate the clinical and hemodynamic outcomes in patients with prosthesis-patient mismatch (PPM) after transcatheter aortic valve implantation (TAVI) with CoreValve (CV) and Sapien XT (XT) valves.

**Methods:** Clinical assessment and echocardiographic parameters were recorded at baseline and prior to discharge in 137 patients undergoing TAVI. PPM was defined as indexed effective orifice area (EOA) <0.85cm²/m².

**Results:** From the 137 patients, 57 (41.6%) had prosthesis-patient mismatch. Among patients with CoreValve 36 (45%) had PPM, whereas 21 (36.8%) patients with the Sapien XT had PPM (p=0.21). Severe PPM was present in 7.5% in CV patients and in 5.3% in XT patients (p=0.62). The procedural success rate was 100% and device success rate was 96%. There was a significant reduction in mean (50.03±14.13 to 9.4±4.15 mmHg, p<0.001) and peak gradients (84.3±20.29 to 18.03±7.8 mmHg, p<0.001) as measured by echocardiography. The EOA was significantly increased (0.66±0.15 to 1.66±0.45 cm², p<0.001), as was the EOA (0.37±0.1 to 0.93±0.29 cm², p<0.001). The Table depicts the impact of PPM on echocardiographic parameters post TAVI in patients with CV and XT.

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>PP vs. No PPM</th>
<th>PP vs. No PPM</th>
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<tr>
<td><strong>EOA</strong></td>
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<tr>
<td>CoreValve</td>
<td>0.85±0.15</td>
<td>0.93±0.29</td>
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<tr>
<td>Sapien XT</td>
<td>0.85±0.15</td>
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**Conclusion:** Patients who underwent TAVI and had PPM were not associated with an adverse hemodynamic outcome before discharge.

**P4194**

Predictors of prosthesis-patient mismatch in patients undergoing TAVI with CoreValve and Sapien XT

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**Purpose:** In transcatheter aortic valve implantation (TAVI), the differences in predictors of prosthesis-patient mismatch (PPM) between CoreValve (CV) and Sapien XT (XT) valves have not been investigated.

**Methods:** Procedural, clinical and echocardiographic parameters (aortic valve annulus diameter, left ventricular ejection fraction (LVEF), pulmonary artery systolic pressure (PASP) defined as moderate if pulmonary artery systolic pressure 31mmHg and severe if PASP<55mmHg, transvalvular gradients, and effective valve orifice (EOA) were recorded at baseline and prior to discharge in 137 patients undergoing TAVI with the CV or the XT valves. PPM was defined as indexed effective orifice area (EOA) <0.85cm²/m².

**Figure 1. ROC curves for significant AR prediction**
Results: There was a significant reduction in mean (50.0±14.13 to 9.4±4.15 mmHg, p<0.001) and peak gradients (84.3±20.29 to 18.03±7.8 mmHg, p<0.001). From the 137 patients, 57 (41.6%) had prosthesis-patient mismatch. Among patients with CoreValve implantation 36 (45%) had PPM, whereas 21 (38.6%) patients with Sapien XT implantation had PPM (p=0.21). Severe PPM was present in 7.5% in CV patients and in 5.3% in XT patients (p=0.62). In the CoreValve group, predictors of PPM included only preprocedural EOAi (OR: 0.002, CI: 0.001-0.688, p=0.005). In the Sapien XT group, baseline LVEF (OR: 0.948, 95%CI: 0.899-0.999, p=0.05) and baseline PASP (OR: 0.954, 95%CI: 0.913-0.996, p<0.05) were unadjusted predictors statistically significant prognostic factors for PPM. Following adjustment for age, baseline LVEF (OR: 0.948, 95%CI: 0.899-0.999, p=0.05) and baseline PASP (OR: 0.954, 95%CI: 0.912-0.997, p<0.05) remained predictors of PPM. Procedural factors were not associated with PPM in either valve.

Conclusions: PPM is a frequent finding in the TAVI era. Predictors of PPM differ between the CoreValve and the Sapien XT valve, and are mainly associated with the severity of stenosis at baseline in CoreValve and with the functional capacity of the left ventricle in Sapien XT.

P4195 Impact of valve type and annular size on post TAVI aortic valve regurgitation

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Purpose: Transcatheter Aortic Valve Implantation (TAVI) is becoming the mainstay of treatment for high-risk and inoperable patients with aortic valve stenosis. Aortic valve regurgitation (AVR) is a common finding following TAVI. We studied the association of post TAVI AVR with the valve type, size and annular size.

Methods: Between April 2009 and January 2012, TAVI was performed in 137 (80 CV and 57 ES) high-risk patients with severe aortic stenosis (age: 79.9±6.89 years; logistic Euroscore 23.15±12.28%: 58.4% female; NYHA III 78.1%; aortic valve mean gradient 50.01±2.04mmHg vs 20.65±12.28%; 58.4% female; NYHA III 78.1%; aortic valve mean gradient 50.01±14.13mmHg). AVR was evaluated based on the American Society of Echocardiography classification (mild, moderate, severe).

Results: Annular size was greater in patients with CV compared to patients with ES (22.54±2.04mm vs 20.65±1.82mm, p<0.01). Mean annular size in 22mm ES was 20.04±1.44mm vs 22.22±1.79mm in 26mm ES (p<0.01). Mean annular size was 20.78±0.84mm in 26mm CV vs 24.37±1.11 in 29mm CV (p<0.01). Patients with CV had greater rates of moderate-to-severe AVR compared to ES (37.5% vs 14%, p<0.01). Figure). Patients with severe AVR had a median annular size of 25.33±0.57mm compared to those with moderate AVR who had 22.19±1.93mm, p<0.009.

Conclusions: Post TAVI AVR is more common in patients with greater aortic valve annular size. Furthermore, patients receiving the CoreValve have greater degree of AVR after implantation.
Methods: We measured Baseline BNP, peak BNP within 48 hours after TF-AVI and predischARGE BNP in 104 patients with complete 1-year follow-up. Results: BNP was elevated at baseline (298.2, IQR 145.8, 661.6 pg/ml) and showed an acute increase after TF-AVI (508.9, IQR 253.3, 866.9 pg/ml) followed by regression towards baseline levels prior to discharge (327.2, IQR 159.2, 634.6 pg/ml), p < 0.001. Acute BNP increase (ΔBNPpeak–baseline) is significantly higher in 30 days non-survivors (277.1 IQR 256.1, 810 pg/ml) than in survivors (132.8 IQR -10.1, 301 pg/ml), p = 0.028, and is found to be an independent predictor of 30 days survival. Kaplan-Meier (KM) survival analysis showed a reduced 30 days survival in patients with a ΔBNPpeak–baseline > 248.9 pg/ml, p = 0.002. For 1-year survival, predischARGE BNP level (250.8, IQR 152.9, 621.9 pg/ml in survivors vs. 591, IQR 354.5, 788 pg/ml in non-survivors, p = 0.002) and ΔBNPdischarge-baseline (211.8 IQR -521.5, -91.1 pg/ml in survivors vs. 108.4 IQR 12.2, 272.6 pg/ml in non-survivors, p = 0.002) are independent predictors. KM analysis showed that 1-year survival is significantly lower in patients with a predischARGE BNP > 327.2 and a ΔBNPdischarge-baseline > -38.3 than in those not fulfilling both criteria, p < 0.001.

Conclusions: BNP values are elevated in patients undergoing TF-AVI. They further increase acutely after procedure and regress to baseline levels prior to hospital discharge. Acute BNP increase is an independent predictor of reduced 30 days survival, while reduced 1-year survival is predicted by higher predischarge BNP levels and failure of BNP to decline at discharge below baseline BNP level.

P4200 Decrease in sheath size for transfemoral Aortic Valve Implantation: what are the consequences? C. Tron, B. Borz, M. Godin, A. Canville, C. Hauville, P.-Y. Litizier, J.-P. Bessou, A. Criber, H. Ettchaninoff. University Hospital of Rouen Hospital Charles Nicolle, Rouen, France

Background: Vascular complications are frequent and remain a recognized limitation of transcatheter aortic valve implantation (TAVI), associated with increased morbidity and mortality. Whether the recent reduction in sheath size has led to a decrease in vascular complications is unknown.

Methods: Since May 2006, 250 consecutive patients underwent TAVI with the Edwards SAPIEN prosthesis in our institution using either the transfemoral (TF, n=190), or the transapical (TA, n=60) approach. Suitability for TF was based on ilio-femoral angiography and computed tomography of the iliofemoral access. Up to October 2009, TF Edwards SAPIEN (ES) implantation required 22 or 24F sheath, inserted surgically in 100% of cases, whereas the SAPIEN XT (SXT) prosthesis was compatible with reduced sheath size of 18 or 19F inserted percutaneously with pre-closure (Prostar XL, 10F) in 98% of cases. The consequences on vascular complication are reported according to the VARC classification.

Results: TF TAVI was performed using ES prosthesis in 78 pts and SXT in 112 pts. All baseline characteristics were similar in the two populations, except the Log EuroSCORE, lower in the SXT cohort (18.4 vs 27.7%, p<0.0001). The ilio-femoral minimal lumen diameter was significantly smaller in the SXT group (7.1±1.1 mm vs 8.8±1.3 mm, p<0.004). There was no difference in the rate of major vascular complications (ES: 7.7% vs SXT: 8.1%) whereas incidence of minor vascular complications was higher in the SXT cohort (18.9% vs 9%, p<0.05). Vascular complications required urgent vascular surgery in 7 cases (3.7%, ES: n=4, SXT: n=3), and covered stent in 12 (6.3%, all in the SXT group). Interestingly, the rate of TA TAVI significantly decreased from 37% in the ES era to 6.9% after onset of the SXT prosthesis (p<0.05).

Conclusions: The reduced sheath size used for Sapien XT implantation did not decrease the risk of major vascular complications after TF TAVI but increased the rate of minor vascular complications. However, smaller sheath sizes allowed a decrease in the risk of vascular complications in the subclavian versus femoral group (30.7±15 vs. 18.5±12, P = 0.001 and 10.9±5.6 vs. 7.5±5, P = 0.01, respectively), had more comorbidities (Charlson index 5.4±1.9 vs 3.5±1.8, P = 0.001) even though the subclavian group were younger (76±6.7 vs. 79.5±6.2 P = 0.019) and they had a higher rates of porcelain aorta than femoral group (21.7% vs. 6.5%, P<0.01). Mortality at 30 days was 8.7% for subclavian group and 4.7% for femoral group. P = 0.40; after a mean follow-up of 16.4±11 months, the survival was 80% for subclavian group vs. 80.8% for femoral group, P = 0.13.

P4201 Lower pacing rate with CoreValve TAVI: high implantation or Accutrak catheter, or both? M. Drury-Smith, S. Lakshmanan, R. Giri, M. Fayaz, J. Cotton, M. Bhabra, S. Khogali. Heart and Lung Centre, Wolverhampton, United Kingdom

Introduction: Permanent pacemaker implantation (PPI) post transcatheter aortic valve implantation (TAVI) is a well recognised complication and the greater requirement after CoreValve TAVI compared with surgery (33% vs 8%) has caused concerns. Pre-existing bundle branch block (BBB), larger valve size, post dilatation and low implantation have been shown independently increase the risk of PPM requirement. Implantation below the aortic annulus can result in compression of conduction tissue and heart block. A modified delivery catheter (ACCUTRAN) may allow a more controlled release expansion of the prosthesis, preventing low implantation and reducing PPM need. We evaluated the PPM requirement in all our TAVI patients (pts) treated before and after the introduction of the Accutrak catheter.

Methods: TAVI was performed in 101 pts: trans-femoral (80 pts), left subclavian (16 pts) and direct aortic approach (5 pts). A high valve deployment strategy of 3-5 mm below the aortic annulus was routinely employed. 12 of these had a pre-existing PPM and were excluded from analysis. 43 of the remaining 89 underwent TAVI using the Accutrak catheter. Procedural outcomes were analysed (table) Results: Recognised predictors of PPM requirement post TAVI, were similar in both groups and were not significant (table). A total of 9 patients required a new

Incidence and prognostic implications of the subclavian approach for Transcatheter aortic valve implantation with the CoreValve prosthesis

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Transcatheter aortic valve implantation is an alternative option for patients with severe aortic stenosis at high surgical risk. The main approach is the femoral artery but in some cases it is not favorable by inadequate iliofemoral anatomy or extensive disease, so subclavian artery approach may be feasible. The aims of this study were to report the frequency of the subclavian approach and its relation to the clinical outcome after transcatheter aortic valve implantation.

Methods: Between April 2008 and January 2012, the CoreValve prosthesis (Medtronic, Minneapolis, MN, USA) was implanted in 239 consecutive high-risk surgical patients with symptomatic severe aortic stenosis. The subclavian approach was used in 28 patients (9.9%).

Results: The median logistic EuroSCORE and STS scores were significantly higher in the subclavian versus femoral group (30.7±15 vs. 18.5±12, P = 0.001 and 10.9±5.6 vs. 7.5±5, P = 0.01, respectively), had more comorbidities (Charlson index 5.4±1.9 vs 3.5±1.8, P = 0.001) even though the subclavian group were younger (76±6.7 vs. 79.5±6.2 P = 0.019) and they had a higher rates of porcelain aorta than femoral group (21.7% vs. 6.5%, P<0.01). Mortality at 30 days was 8.7% for subclavian group and 4.7% for femoral group. P = 0.40; after a mean follow-up of 16.4±11 months, the survival was 80% for subclavian group vs. 80.8% for femoral group, P = 0.13.

Conclusions: The subclavian approach is not frequent in patients undergoing transcatheter aortic valve implantation with the CoreValve prosthesis and appeared safe for the patients at very high or prohibitive surgical risk, including porcine aorta patients, with contraindications to the femoral approach.
Hybrid endovascular repair for aortic arch pathology: intermediate outcomes and complications

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Objectives: To evaluate the outcomes of hybrid endovascular repair for aortic arch pathology.

Methods: This study was a retrospective analysis involving patients who underwent hybrid endovascular repair for aortic arch pathologies.

Results: Twenty-one patients (16 men; mean age, 64.7±16.2 years) with aortic arch pathologies were treated by hybrid endovascular repair. The indications for treatment included increased aneurysm size in 16 cases (71.4%), rupture or impending aneurysmal rupture in 5 cases (23.8%), and rapid growth of aortic dissection in 1 case (4.8%). Supra-aortic vessel transposition and stent-graft implantation were achieved in all cases. Two types of stent-graft were used, as follows: the Seacher thoracic stent-graft in 14 patients (66.7%); and the Valiant stent grafts in 7 patients (33.3%). Peri-operative complications affected 5 patients (23.8%), as follows: bleeding (n=4, 19.0%); stroke (n=3, 14.3%); renal failure (n=2, 9.5%); vascular injury (n=1, 4.8%); and respiratory failure (n=1, 4.8%). Two patients died within 30 days (9.5%). Technical success was achieved in 15 patients (71.5%). Early endoleaks were noted in 4 patients (19.0%). One patient died during follow-up (mean, 21.3±11.6 months) due to a de novo aortic dissection. Persistent early endoleaks were noted in 4 patients (19.0%); 2 of the 4 patients were successfully managed with implantation of additional stent-grafts. No late onset endoleaks were noted. The death-free survival and re-intervention-free survival rates during follow-up were 85.7% and 90.5%, respectively.

Conclusion: Hybrid treatment with supra-aortic vessel transposition and endovascular repair may be an option in frail patients in whom open procedures is too risky.

PPM (10.1%) post TAVI. There were no significant differences in PPM requirement in “middle to low” implanting centres is required.

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Early changes of left ventricle deformation indices after transcatheter aortic valve implantation: A speckle tracking echocardiographic study

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Purpose: Transcatheter aortic valve implantation (TAVI) has been established as a reliable alternative treatment in high risk patients, resulting in symptoms and left ventricle function improvement. The aim of this study was to evaluate the impact of TAVI on early recovery of left ventricle function using echocardiographic left ventricular deformation parameters and to define their possible correlation with myocardial function.

Methods: In 16 patients (8 females, 81±5 years; EuroScore: 24±4%) with severe aortic stenosis but free of significant coronary artery disease who underwent TAVI with the CoreValve® System at discharge. Deformation indices of left ventricle such as Peak Systolic Longitudinal Strain (PSSLs) and Torsion (apex-basal rotation) were determined by speckle tracking echocardiography using commercially available computer software. Besides, Left Ventricle Ejection Fraction (LVEF), calculated with Simpson method, was evaluated at one month follow-up.

Results: In all patients at discharge, a reduction of transaortic peak pressure gradient (p<0.0005), of mean pressure gradient (p<0.0001) were observed, with a concomitant increase in aortic valve area (p<0.0001). In addition, 2D speckle analysis showed a significant improvement of PSSLs at discharge (-10.6±2.8 vs -13.7±3.9, p=0.008). Similarly, left ventricular torsion was significantly increased comparing to pre-implantation values (7.2±5.1 vs 11.5±6.1, p<0.015). However, overall LVEF did not change (51.4±8.8 vs 50.9±8.1; p=0.50). Curving follow-up, a strong correlation was found between discharge PSSLs and one month LVEF, with greater longitudinal deformation (PSSLs) associated with higher LVEF (p<0.03). However, one month LVEF compared to discharge, indicated a trend for improvement (p<0.05), but not statistically significant.

Conclusions: Deformation indices of PSSLs and Torsion are able to detect early improvement of left ventricle function after TAVI regardless LVEF alteration. Moreover, PSSLs seems to predict LVEF in one month. Larger studies with long term follow-up are required.
Mitral regurgitation after transcatheter aortic valve implantation with the Medtronic-CoreValve prosthesis

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**Background:** Mitral regurgitation (MR) is a risk factor on long-term survival in elderly patients who underwent an aortic valve replacement (AVR). The impact of mitral regurgitation in patients who undergo transcatheter aortic valve implantation (TAVI) is unknown. The aim of the study was to assess the influence of MR on survival in TAVI patients treated with a Medtronic-CoreValve prosthesis.

**Methods:** In this single center prospective observational study we included 100 patients (age 81±6 years, 40 male) with severe symptomatic aortic valve stenosis who underwent TAVI with the Medtronic-CoreValve bioprosthesis and underwent a post procedural echocardiographic evaluation. Other clinical parameters were obtained from the medical history.

**Results:** From the patients with an MR grade >3 (n=94) pre-procedural, 14% increased to MR grade ≥3 after TAVI (p=0.002) and from 6 patients with moderate to severe MR pre-procedural only one patient had a MR grade ≥3 after TAVI. Forty percent of the patients with significant (grade ≥3) MR died within 1 year versus 20% of the patients with MR grade <3 (p=0.051); 30-day mortality and 30-day cardiovascular mortality were not influenced by MR grade ≥3 following TAVI.

**Conclusion:** After TAVI with a CoreValve prosthesis there is a significant increase in MR grade in patients with MR grade >3. One year survival shows a tendency to be impaired in patients with a significant MR post TAVI.

Renal outcome after transcatheter aortic valve implantation

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**Background:** Renal function impairment is a frequent complication after cardiac valve implantation procedures. Data on risk factors for renal impairment after transcatheter aortic valve implantation (TAVI) are limited.

**Methods and Results:** In 299 consecutive TAVI patients (mean age 80±3.7±12 years: 54.8% women) we assessed renal function through plasma creatinine measurement and estimated glomerular filtration rate at baseline, peak during 72 h post procedure and at discharge and monitored individuals for incident renal failure (none, 213 (71.2%); stage 1 renal impairment, 62 (20.7%); stage 2, 15 (5.0%); and stage 3, 9 (3.0%). Mean creatinine concentrations in the sample were 1.10 (0.96-1.50) mg/dl at baseline and MDRD estimated glomerular filtration rate resulted in 56.63±23.30 ml/min/1.73 m². As expected, logarithmically transformed baseline creatinine was related to incident renal failure (Odds ratio [OR] 1.91, 95% confidence interval [CI] 1.19-3.10, p=0.007). Correlates of renal failure besides age and sex in age and sex-adjusted logistic regression analyses were body mass index (OR 1.09 95% CI 1.03-1.15, p<0.001) and logistically transformed procedure time (OR 2.24, 95% CI 1.08-4.70, P=0.03). In linear regression analyses procedure time was strongly related to peak change in glomerular filtration rate.

**Conclusions:** Besides age and sex, body constitution and procedure time are correlates of acute kidney injury after TAVI. When assessing periprocedural risk factors in TAVI patients, body mass index should be considered in particular in elderly patients with pre-existent renal impairment.

Predictors of mortality post balloon aortic valvuloplasty, results from the BRAVO registry

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**Purpose:** There have been notable advances in balloon aortic valvuloplasty (BAV) technique including RV pacing and improved management of the large sheath access site. However, a subgroup of patients continues to have poor outcomes despite intervention, and prognostic variables have not been identified in a contemporary context. We sought to examine the correlates of 1-year mortality from a recent BAV registry.

**Methods:** We conducted a retrospective review of patients who underwent non-emergent, retrograde BAV at two high volume centers from 1/1/2005 - 12/1/2010. Baseline demographic, laboratory, hemodynamic, and procedural characteristics were compared according to 1-year survival post-index BAV procedure.

**Figure 1:** 1-year impact of LTB after TAVI
Trans-catheter Aortic Valve Implantation (TAVI)

Objective: To evaluate incidence and predictors of combined safety endpoints occurring after transcatheter aortic valve implantation (TAVI) with current commercially available prostheses.

Methods: We enrolled consecutive patients undergoing TAVI with Edwards-Sapien XT (n=50) or Medtronic CoreValve (n=720) from a single Centre experience. The following parameters were quantified in both atria and ventricles: Strain (S), systolic strain rate (SRS), diastolic systolic rate (SRE), strain rate (SRR), longitudinal strain (GLS) and torsion using speckle tracking echocardiography (c) and tissue Doppler imaging (a). For the right atrium, S and SRS were quantified. To serve during hypoxic exercise is reduced in LV. In addition, hypoxia had an impact on the ratio of passive conduit to active contraction phase in right atrium. The contractile reserve during hypoxic exercise is reduced in LV. In addition, hypoxia had an impact on the ratio of passive conduit to active contraction phase in right atrium.

Conclusions: Exposure to normobaric hypoxia leads to an increase of LV overall twist and regional myocardial deformation in both ventricles. The contractile reserve during hypoxic exercise is reduced in LV. In addition, hypoxia had an impact on the ratio of passive conduit to active contraction phase in right atrium.
Myocardial function left ventricular deformation

Prognostic significance of speckle tracking-derived myocardial function in multivessel coronary disease

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Purpose: We aimed to identify prognostic factors in unsel ected cohort of patients with multivessel coronary disease (MCD) among parameters derived from: state of the art echocardiographic assessment including speckle tracking echocardiography (STE), functional exercise testing and 6-min walk test (6MWt) and full biochemistry panel including beside traditional risk factors N-TproBNP, CRP, HbA1c, thorombomodulin, von Willebrand Factor, and cardiography (24h). STE indexed to diastolic filling curve and 2D strain imaging (2DSE) were performed in order to assess the occurrence of primary end point: End1 (all cause death or myocardial infarction) and secondary end point: End2 (mortality, myocardial infarction, cardiac hospitalization or need for unplanned revascularization). Mean LVEF was 49.9 ± 10.2% and predominant angina class was CCS III (68%). The management was individualized based on heart team decision resulting in 55% angioplasty rate and 22% bypass grafting rate.

Results: There were 3 deaths (3.6%), 12 MI (14%), 4 ischemic strokes (5%), 6-min walk test (6MWT) and full biochemistry panel including beside traditional risk factors N-TproBNP, CRP, HbA1c, thorombomodulin, von Willebrand Factor, and cardiography (24h). STE indexed to diastolic filling curve and 2D strain imaging (2DSE) were performed in order to assess the occurrence of primary end point: End1 (all cause death or myocardial infarction) and secondary end point: End2 (mortality, myocardial infarction, cardiac hospitalization or need for unplanned revascularization). Mean LVEF was 49.9 ± 10.2% and predominant angina class was CCS III (68%). The management was individualized based on heart team decision resulting in 55% angioplasty rate and 22% bypass grafting rate.

Conclusions: The results of our study confirm the importance of established systemic risk factors: hyperglycemia defined by HbA1c and inflammatory condition (leukocytes). However, novel echocardiographic parameters derived by STE, especially GLS and left ventricle torsion, emerge as predictors of adverse outcome superior to traditional echocardiographic indices. Novel biomarkers and functional exercise tests did not prove promising usefulness in this group of patients.

P4215

Correlation of area strain by three-dimensional speckle tracking echocardiography with exercise capacity in subjects undergoing treadmill exercise test

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Purpose: Area strain is a new index for left ventricular deformation measured from 3-dimensional speckle tracking echocardiography (3D STE). However, its clinical significance has rarely been studied.

Methods: This study included 40 healthy subjects who undergoing regular health examination. All of the subjects did not have coronary artery disease or any structure heart disease and were free of symptoms. Global area strain (GAS) from 3D STE was measured by 2D-dimension speckle tracking echocardiography (2D STE). Exercise capacity was limited by Bruce’s protocol (Re (VO2), WbC, HbA1c, GAS were assessed before and after 30 min exercise).

Results: One subject was excluded due to poor 3D image. The remaining 39 subjects (age 50.9 ± 9 years, 27 men) formed the basis of this study. Total exercise time was 54.5 ± 10 seconds. GAS was significantly correlated with exercise time (r = 0.502, p = 0.001) but not left ventricular ejection fraction (r = 0.129, p = 0.434). GLS (r = -0.231, p = 0.157) and early diastolic mitral filling velocity to annulus velocity ratio (E/e’; r = -0.284, p = 0.079). There were 3 subjects with impaired exercise capacity, GAS from 3D STE was correlated with exercise capacity in apparent healthy subjects but not GLS from 2D STE.

P4214

Left ventricular rotation and torsion and its relation with functional capacity in hypertensive patients

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Purpose: In patients (pts) with hypertension (HA) left ventricular (LV) apical rotation at rest and LV torsion can be predictors of LV functional reserve. The aim of our study was to assess the relationship between apical rotation and torsion of LV at rest and functional capacity in pts with HA.

Methods: We studied 50 hypertensive aged 50±11 years, 16 women and 24 men, with slightly elevated body mass index (28.1±3 kg/m²) and first/second degree hypertension. We performed standard two-dimensional and Doppler echocardiography (2DE) and cardiopulmonary exercise testing (CPET) using “breath by breath” method, measuring oxygen uptake (VO2) at anaerobic threshold (AT).

Results: In our pts with preserved LV systolic function 8 pts had normal dias tonic function and 32 had diastolic dysfunction of first/second degree, 22 pts (55%) had concentric remodeling. We found following average values of 2DE and 4DE parameters: left atrial diameter 39.7±3.9mm, relative wall thickness 0.44±0.07, end-systolic volume 51.5±13.53ml, end-diastolic volume 109.3±26ml, LV ejection fraction 56±3.5%; apical rotation 5.87±3.26deg, apical rotation ratio S-Wave 48.46±19.95deg/s, apical rotation ratio E-Wave 46.88±22.16deg/s, apical rotation ratio A-Wave 31.51±16.28deg/s, apical circumferential strain -12.5±6.2%, LV torsion 10.05±4.2deg. Average VO2 at AT was 18.92±4.71ml/kg/min.

We established significant negative correlation between VO2 at AT and apical rotation (r = -0.361, p=0.028), rotation ratio S-Wave (r = -0.342, p=0.039) and LV torsion (r = -0.433, p=0.08). According to Regression Model apical rotation was selected to be the strongest independent negative predictor of VO2 at AT (β= -0.36, p=0.034). In respect to demographic and 2DE parameters of LV function with significant positive correlation between apical rotation and torsion and age (rotation)=-0.32, p=0.043; torsion)-0.37, p=0.016 and late mitral annular velocity (rotation)=0.32, p=0.042; torsion)=0.38, p=0.013).

Conclusions: Our data showed that older age and diminished LV compliance resulted in increased apical rotation at rest and torsion of LV and also, that namely pts with higher values of apical rotation at rest had lower functional capacity expressed through AT.
**Conclusion:** Delayed LV diastolic relaxation is seen in healthy chronic smokers, even after abstinence from smoking for several hours. Acute smoking inhalation induces a further delay in diastolic relaxation while systolic function is preserved.

**Methods:** In 25 patients with first-time acute ST elevation myocardial infarction, myocardial viability was assessed using 2DSTE and cEMRI to predict recovery of function at 6 months follow-up. For each left ventricular segment in a 16-segment model, peak radial, circumferential and longitudinal strain was determined using 2DSTE (EchoPAC, GE Ultrasound, Horton, Norway), and the relative extent of hyperenhancement using cEMRI.

**Results:** Of 129 segments with impaired function early after AMI, 65 showed regional recovery. Compared with segments showing functional improvement, those that failed to recover had lower peak radial (18.1±26% vs. 34.2±22%; p<0.001), circumferential (29.7±10% vs. 48.4±13%; p<0.001) and longitudinal (9.0±5% vs. -13.5%; p<0.001) strain and a greater extent of hyperenhancement (71±21% vs. 25±20%; p<0.001). Among strain parameters, circumferential strain yielded greater area under the curve (0.914) than radial and longitudinal strain (0.717 and 0.743, respectively). The predictive value of circumferential strain (sensitivity 80.3%, specificity 81.2%, at a cutoff value of 12.5%) could be comparable to that of hyperenhancement by cEMRI (sensitivity 87.8%, specificity 88.1%, area under the curve 0.935, at a cutoff of 46% hyperenhancement).

**Conclusions:** Myocardial deformation imaging based on 2DSTE is a powerful novel modality to identify reversible myocardial dysfunction after AMI.

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**Background:** Soluble angiotensin converting enzyme (sACE) in treated hypertensives.

**Methods:** In 220 untreated patients (age=54±11 years) with essential hypertension and 80 healthy controls, we measured a) LV longitudinal, circumferential and radial strain (S), peak torsion and the percentage changes between peak twisting and untwisting at mitral valve opening and end of early diastolic filling using speckle tracking echocardiography b) Carotid to femoral arterial pulse wave velocity c) Oxygenation of arterial stiffness (G) plasma levels of sACE.

**Results:** Compared to controls, patients had decreased longitudinal strain (-19.2±2.6 vs. -21.9±2.5 p<0.01), peak torsion (13.8±4.3 vs.15.7±3.6 deg p<0.05), % changes between peak twisting and untwisting at mitral valve opening (29.8±18 vs. 38.7±5.0 p<0.05) as well as at end of early diastolic filling (67.9±9 vs. 73±8%, p<0.05), higher PWV (10.5±1.8 vs 8.2±1.5, p<0.01) and higher sACE levels (27.8±8 vs.21.7±4 U/ml p<0.05). Increasing sACE was related reduced radial S, peak torsion and % change between peak twisting and untwisting at end of early diastolic filling using (r=0.41, r=0.40, r=0.37, respectively, p<0.05) By re- analysis the above relations remained significant after adjustment for age, sex, mass and blood pressure (p<0.01). No association was observed between SACE and PWV (p>ns)

**Conclusions:** Soluble angiotensin converting enzyme is related to impaired myocardial deformation and torsion in untreated hypertensive.

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**Background:** Three-dimensional speckle tracking imaging (3DS) allows assessment of left ventricular (LV) volume and function with high sensitivities. However, it is still unclear whether feasibility of regional data collection and estimates of regional strain differ between 3DS and two-dimensional speckle tracking imaging (2DS). We examined this issue in the present study.

**Methods:** Standard 2D echocardiography and 3D data set collection by using Vivid E9 with 4V probe (GE Healthcare) were performed in 212 subjects, who participated in an annual health examination. Apical long axis, four chamber and two chamber views were recorded to assess longitudinal strain by 2DS. 3DS and 2DS were analyzed off line by EchoPAC (GE Healthcare). We excluded subjects in whom 4 or more of 18 LV segments were unsuitable for strain determination, and 49 subjects (all women, age 63±12 years) contributed to the present analysis.

**Results:** The feasibility of 3DS was lower at LV base level (Figure). There were significant differences between strain by 3DS and longitudinal strain by 2DS in the mid-anteroseptum (-25.3% vs. 21.4%, p<0.0001), mid-lateral (-18.1% vs. -24.3%, p<0.0001), mid-posterior (-23.7% vs. -18.9%, p<0.0001) and mid anterior strain (-25.9% vs. -19.6%, p<0.0001). Strain in the other segments and global strain were similar in 3DS and 2DS.

**Conclusions:** There are regional differences in feasibility of 3DS and data agreement between 3DS and 2DS. 3DS provides significantly lower estimates of strains in mid-level of the ventricle compared with 2DS.
Assessment of left ventricular myocardial deformation and mechanical dysynchrony in patients with heart failure: insights from three-dimensional wall motion analysis

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Purpose: Impaired myocardial contractility is detected with two-dimensional speckle tracking echocardiography (2DSTE) in heart failure patients with normal ejection fraction (HFNEF); however, 2DSTE is limited by ignorance of actual three-dimensional myocardial motion. Therefore, this study is aimed to further explore the myocardial function including the global dysynchrony in HFNEF with three-dimensional speckle-tracking echocardiography (3DSTE) which circumvent the limitations of 2DSTE.

Method: We enrolled thirty-three healthy subjects (48±12 years; 48.5% male), 53 patients with HFNEF (70±10 years; 56.6% male) and 41 with reduced ejection fraction (HFREF) (65±10 years; 87.5% male) in our study. 3D-STE was performed (Toshiba Medical Systems, Japan) to obtain global area strain (AS), longitudinal (LS), circumferential (CS) and radial strain (RS). For LV dysynchrony, AS-systolic dyssynchrony index (AS-SDI) was calculated from the standard deviation of the time to peak segmental AS of 16 segments. Transient global AS, LS, CS and RS in patients with HFNEF were significantly higher than their counterparts with HFREF (all p<0.001) but lower than in the normal group (all p<0.05) (Table 1). Intriguingly, AS-SDI was significantly prolonged in HFREF compared with HFNEF respectively, with the time delay of 1.10±0.10 ms vs. 74.9±18.9 ms vs. 37.5±16.3 ms; both p<0.001 vs. control, and was more severe in the HFREF group (p<0.001). Based on normal cutoff value of ≥ 68ms, the prevalence of LV systolic dysynchrony was significantly higher in HFREF than that in patients with HFNEF (61.0% vs. 20.8%; chi-square =15.83, p<0.001).

Comparisons of 3D-echocardiogram data

<table>
<thead>
<tr>
<th>Normal (n=33)</th>
<th>HFNEF (n=53)</th>
<th>HFREF (n=41)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global AS (%)</td>
<td>-48.3±6.5</td>
<td>-44.0±7.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global CS (%)</td>
<td>-36.2±6.9</td>
<td>-32.8±6.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global LS (%)</td>
<td>-16.6±3.5</td>
<td>-14.5±3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global RS (%)</td>
<td>30.7±10.7</td>
<td>24.8±11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AS-SDI (ms)</td>
<td>35.7±16.3</td>
<td>29.2±12.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.001 versus control.

Conclusions: As a combination of both LS and CS, not only can 3D-derived global AS accurately detect subtle myocardial dysfunction in HFNEF, it can also assess LV dysynchrony more comprehensively in a 16-segmental mode during one cardiac cycle, which might be promising for further exploring the pathophysiology of HFNEF.

Area strain for the assessment of regional left ventricular wall thickening using 3D Speckle Tracking

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Background: 3D speckle tracking is a promising new technology. It allows reconstructing LV motion in time and space. Shortening in the longitudinal and circumferential directions can be combined in an area strain (aS) measurement which in contrast to wall thickening (radial strain) does not require endo- and epicardial border detection. We investigated the relationship between aS and wall thickening by two geometrically independent measurements.

Methods: In 12 patients, 3D full volume echocardiographic clips of the LV were acquired. 3D endo- and epicardial border detection was performed to calculate wall thickening, whereas 3D speckle tracking was used to assess aS. All geometric measurements were performed frame-by-frame at 336 sites on refined meshed grids.

Results: 52±7.25 wall thickness = aS data pairs were retrieved. In ROC analysis, an aS > -15.3% was able to detect a systolic wall thickening > -20% with a sensitivity and specificity of 83.2% and 80.2%, respectively. The area under the ROC curve was 0.88. As expected from deformation theory, there was a nonlinear relation between wall thickening and aS (Poission effect). The estimated Poisson’s ratio associated with myocardium was 0.39, showing even myocardium is not perfectly elastic and incompressible (i.e.<0.50), but exhibits a volume loss during systole.

Conclusion: aS derived from 3D speckle tracking reflects local wall thickening during the cardiac cycle and has the potential to detect regional contraction abnormalities. In principle, aS can be converted directly into radial strain using basic elastic deformation formulas (Poission effect), but the compressible nature of myocardial tissue should be considered by applying a Poisson’s ratio below 0.50.

Myocardial function left ventricular deformation


Purpose: Endoventricular resection (EVR) is the preferred treatment for patients (pts) with type II diabetes (DM).

Method: We performed stereoscopic fundus photography with 7 standard fields in 114 type 2 DM pts (62.9±10 years, 53% female) without overt CVD. Detailed transcorneal ophthalmoscopy with two-dimensional speckle tracking imaging was performed to measure global left ventricular (LV) function, including longitudinal strain and strain rate.

Results: The incidence of non-proliferative and proliferative retinopathy was 22% (19%). There were no significant differences in age (63.6± vs. 62.1±, female gender (50 vs. 56%), fasting glucose (7.5±2.5 vs. 7.4±1.9 mmol/L) and Hba1c (8.0±1.3 vs. 7.6±1.2%) between pts with or without DR (all p>0.05). However, pts with DR had a longer disease duration than pts without DR (14.8±3.7 years, P<0.01). Conventional ophthalmoscopy showed no differences in LV ejection fraction (63.6±64.8%) and LV mass index (200±47 vs. 203±62 gm²/m²) between the 2 groups (P=0.05). However, pts with DR had a significantly lower LV global longitudinal strain (-18.3±2.11 vs. -18.5±P=0.05) and strain rate (-84.0±15.5 vs. -90.5±3.33, P<0.05) compared with pts without DR. After adjustment with age, gender, Hba1c, duration of disease and conventional cardiovascular risk factors, multivariate linear regression revealed that DR was independently associated with impaired LV global longitudinal strain rate (p=0.28, confidence interval [CI]=0.07 to 0.30, P<0.01), but not LV global strain (p=0.18, CI=0.22 to 0.20, P=0.09).

Conclusion: Our results demonstrated that DR was detected in 19% of type 2 DM pts without overt CVD. The occurrence of DR was independently associated with subclinical LV myocardial dysfunction as detected by two-dimensional speckle tracking imaging. The findings of the study suggested that microvascular...
Ejection fraction and deformation in response to three different chemotherapeutic regimens

Methods: We enrolled 35 consecutive patients (average 56.1±12.9: 32 males) with a first STEMI undergoing PCI within 12 hours of symptoms onset. Anagrelide was considered as a first-line antithrombotic agent in the following cases: left atrial thrombus, severe mitral regurgitation, atrial fibrillation, past history of atrial fibrillation, and presence of atrial flutter or atrial tachycardia. Results: The average interval between the last dose of anagrelide and PCI was 2.6±1.3 hours (range 0.5−6.7). Conclusions: Anagrelide is an effective and safe drug for the prevention of thrombotic complications in patients undergoing PCI.
by speckle tracking derived right ventricular (RV) and left ventricular (LV) global longitudinal peak systolic S and SR, obtained before, early after and at 1 month follow-up after RT.

Results: Total radiation dose delivered was 51.7±4.9 Gy in LSBC group, 54.7±9.1 Gy in LSLC group. The mean dose to the heart was 6.3±4.5 Gy and the mean heart volume receiving 30 Gy (V30) was 7.3±6.5% in LSBC group. In pts with LSLC, the mean dose to the heart was 21.3±7.4 Gy and V30 was 30.1±10%. Compared to baseline, RV-S was significantly decreased early after RT and at first month follow-up in both groups (-22.3±4.3 vs. -19.9±3.4 vs. -19.9±3.0, respectively, p<0.01, in LSBC group). RV-SR changed significantly in pts with LSLC (-1.5±7.0 vs. -1.3±6.0 vs. -1.2±0.9, respectively, p=0.192). Interestingly, LV-S decreased significantly in LSLC group (-20.7±4.4 vs. -19.2±3.6 vs. -19.0±3.7, respectively, p=0.03). No decline in LV deformations was observed in pts with LSBC (-20.0±3.0 vs. -19.6±3.0 vs. -19.5±3.2, respectively, p=0.95).

Conclusion: Pts receiving RT for LSBC and LSLC have decreased RV-S whereas LV-S was only reduced in LSLC group following RT. RV-SR was also decreased in pts with LSLC. Reduction in RV-S and SR was likely due to higher radiation exposure of the right ventricle due to its anterior location. Moreover, high dose radiation exposure to heart reduced LV-S in LSLC group. This study demonstrated that RT has a detrimental effect on both RV and LV-SR, is first to be reported.

**P4229**

Reduction in ventricular wall thickness increases the dyssynchrony by speckle tracking strain rate analysis

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Background: Left ventricular (LV) dyssynchrony was reported as a useful index for predicting the response to cardiac resynchronization therapy. However, it has not been clear that which factors influence on the dyssynchrony in patients with electrical dyssynchrony. Thus, we evaluated the degree of LV dyssynchrony in patients with right ventricular (RV) pacing by speckle tracking strain rate analysis (SR analysis).

Methods: Echocardiography was performed in 81 consecutive patients with RV pacing. As a dyssynchrony index, the time difference between 1st peak of LV and RV end-systolic strains (IVS-PW delay) was measured by M-mode at the mid-LV level. We used off-line software Echomovie (GE Ultrasound) for SR analysis and measured radial SR at mid-LV short axis view. DT was defined as the ratio of average myocardial thinning (negative SR) at 6 segments of the ejection period (Figure). Results: Twenty-seven patients were LV ejection fraction (LVEF) >50% (lowEF) and 54 patients were >50% (highEF). Mean value of IVS-PW delay was 30±17ms, and there was no significant difference between IVS-PW delay of lowEF group and that of highEF group (30±15ms vs. 29±18ms, N.S.). DI of lowEF was significantly higher than that of highEF (25±12ms vs. 8±10ms, p<0.001). DI correlated with the LV end-systolic volume (>0.536, p<0.001), QRS duration (>0.408, p<0.01) and LVEF (<0.621, p<0.001). In multivariate analysis, the independent predictor of DI was LVEF (p<0.001).

Conclusions: Dysynchrony in patients with RV pacing was constantly high regardless of LVEF, while dyscoordination was enhanced by reduced LVEF. Reduction in RV-S and SR was likely due to higher radiation exposure of the right ventricle due to its anterior location. Moreover, high dose radiation exposure to heart reduced LV-S in LSLC group. This study demonstrated that RT has a detrimental effect on both RV and LV-SR, is first to be reported.

**P4230**

Effect of left ventricular twisting for the accuracy of two-dimensional longitudinal strain analysis

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Purpose: 2D longitudinal strain (LS) calculation could be influenced by loss of speckles due to left ventricular (LV) twisting motion. 3D speckle tracking echocardiography (STE) is theoretically more accurate for LS measurements. If LV twisting motion affects 2D LS calculation, we hypothesized worst correlation of LS between 2DSTE and 3DSTE was observed at apical level, and best correlation was noted in the middle level due to helical nature of myocardial fibers.

Methods: We acquired 2D apical 4-, 2-chamber and long-axis views and 3D full volume datasets (GE, Vivid E9) in 54 patients with various cardiovascular disease (mean age: 64±18 years, 29 men, LVEF: 54±12%). Using 3D/2D speckle tracking software, global LS and averaged LS at 3 LV levels (basal, middle and apical) were calculated. In 44 of 54 patients who could be also analyzed LV twist on the 2D short axis views, patients were divided into two groups according to the median value of LV twist (13.4 ms duration) for investigating the effect of LV twisting.

Results: A good correlation of global LS was noted between the two methods (2DSTE: -15.8±5.3, 3DSTE: -15.4±4.1, r=0.89±0.01) with no significant bias (0.4±0.1ms). Correlation of averaged LS and their mean bias were 0.52±1.59 at basal level, 0.89±1.17 at middle level and 0.73±0.46 at apical level, respectively. Correlation of global LS between the two methods was higher in group of patients who had LV twist value less than 13.4 degree (r=0.39) compared to group of patients with LV twist value >13.4 degree (r=0.68).

Conclusions: Patients who had higher LV twist revealed moderate correlation of global LS between the two methods. Lower correlation and larger bias of averaged LS at basal and apical LV level between the two methods suggest LV twisting actually affects the calculation of 2D LS.

**P4231**

Assessment of left ventricular dyssynchrony with real time 4D ultrasound system: comparison with Doppler Myocardial Imaging

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Background: Different current echocardiographic methods have been proposed to evaluate left ventricular mechanical dyssynchrony (LVMD). The very latest generation of real-time 4D ultrasound systems (RT4DE) have the ability to acquire a full volume dataset in one cardiac cycle. Aim of the study was to compare the assessment of LVMD by Pulsed Wave- Doppler Myocardial Imaging (PW-DMI) and RT4DE.

Methods: 10 healthy volunteers (NL) and 27 pts with left bundle branch block (QRS wide 147±17ms, EF 38±12%, 68±11%)s and different etiology dilated cardiomyopathy (DCM-LBBB) were studied. RT4DE full volume acquisitions were divided into 16 subvolumes corresponding to the standard myocardial segments to derive time-volume curves for each (TMV). Time to peak contraction (minimum volume) in each segment is normalized for the R-R duration, and 16-SDI/4D is defined as the standard deviation of these timings, expressed as a percentage of cardiac cycle duration. The identification of the latest contracting segment of the LV was studied with TMV Map imaging demonstrating areas of delayed contraction (orange color). Dysynchrony index by PW-DMI was measured as standard deviation of the time from beginning of QR5 to the end systolic velocity in 6 basal segments (6-SDI/4D-PW-DMI).

Results: Data acquisition and analysis with RT4DE was feasible in 35/37 pts (93.1%). The technique provided quick qualitative and quantitative assessment of LVMD in one single heart cycle, during high volumes per second (vps) acquisition (38±14 vps), the latest segmental TMV was of apical basal distribution in 3/25 pts, mild-basal distribution in 7/25 pts, and basal distribution in 15/25 pts respectively. 16-SDI/4D was significantly higher in the DCM-LBBB group compared with NL (9.7±7.4% vs. 4.1±1.7%, p<0.05), there was no difference in 16SDI/4D be-
Brain natriuretic peptide is independently associated with indices of left ventricular filling pressure but not with left ventricular mass in asymptomatic individuals

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Purpose: Measurement of serum natriuretic peptides have been suggested to screen for the presence of left ventricular hypertrophy (LVH) or to track the regressions in LVH. Left ventricular mass index (LVMi) after initiating treatment for hypertension or diabetes. We evaluated the associations of LV mass and serum with serum N-terminal pro brain natriuretic peptide (NT-pro BNP) after adjustment for parameters of LV structure, LV function and LV filling pressure indices.

Methods: Plasma NT-pro BNP concentrations were measured in 1,593 healthy subjects free of manifest cardiovascular disease, recruited from the London Life Sciences Prospective Population (LOLIPOP) study. All subjects underwent comprehensive echocardiography, including tissue Doppler imaging, for measurement of LV mass, LV ejection fraction (LVEF), E/E' and LAVI.

Results: Using stepwise linear regression models, the relationships between diastolic function marker, LV structure, LV function and LV filling pressure indices with NT-pro BNP were explored. Increasing age, male gender and European white ethnicity were independently associated with higher NT-pro BNP. There was an independent association of reduced LVEF (p=0.09, p<0.001), increased E/E' (p=0.12, p<0.001) and increased LAVI (p=0.24, p<0.001) with higher NT-pro BNP. An initial significant association observed between increasing LVMi (p=0.13, p<0.001) and higher NT-pro BNP was subsequently abolished after adjustment for LAVI (p=0.06, p=0.41). Type 2 diabetes, hypertension and the presence of LVH were not significant at time of diastolic function evaluation.

Conclusions: NT-pro BNP is unlikely to be a useful biomarker for the detection of subclinical hypertrophic LV remodeling, being more closely associated with the morphophysiological parameters of increased LV filling pressure and with LVEF.

Decreased velocity propagation of the left ventricle is associated with increased arterial stiffness

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Purpose: Aim of the present study was to evaluate the diastolic performance of the left ventricle, as assessed by velocity propagation, and correlate it with arterial stiffness indexes, in essential hypertensives (EH).

Methods: We studied 113 consecutively newly diagnosed EH patients stage I-Iii (age 51±12, 41% females) without prevalent cardiovascular disease. All patients underwent: a) complete conventional and Tissue Doppler Imaging (TDI) echocardiographic study, b) assessment of heart rate-corrected augmentation index (AIx75) using SphygmoCor, and c) a 24-hour ambulatory blood pressure monitoring (ABPM). The study population was divided into two groups according to the median value of velocity propagation (VP): group A (n=57, VP<5.9cm/sec) and group B (n=56, VP>5.9cm/sec).

Results: The two groups did not differ regarding age, gender, 24hr systolic and diastolic BP. Group B compared to A had significantly higher values of AIx75 and peripheral vascular resistances (29.3±9.5 vs 23.9±11.5%, p=0.016, respectively) and significantly decreased aorta distensibility and cardiac index (0.16±0.1 vs. 0.25±0.2, p=0.04, respectively) and LA ejection fraction (55.7±12.5% vs 58.2±5.4%). LV/E'A' ratio was significantly higher in patients with elevated left ventricular filling pressures (7.1±5.2 vs 3.7±2.5; p=0.03) and LA ejection fraction presented a significant negative correlation with LAVI/A' ratio (r=0.43, p=0.042). Area under the receiver operating characteristic curve to diagnose elevated left ventricular filling pressures by LA ejection fraction was 0.814 (6.635; 0.975).

Conclusion: LA ejection fraction by 3D echocardiography recognizes patients with left ventricular filling pressures, therefore it might be valuable alternative at time of diastolic function evaluation.

The E-wave deceleration rate E/DT but not the tissue-Doppler derived index E/E' reliably characterizes pressure-overload induced diastolic dysfunction

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Background: The ratio of transmural to mural annular early diastolic velocity E/Ea is widely considered the best non-invasive determinant of diastolic function. However, recent studies in patients with diverse heart diseases have delivered highly contradictory results, suggesting that the usefulness of E/Ea might be dependent on the presence of left ventricular hypertrophy.

Methods and results: Rats underwent aortic banding (AoB) to induce pressure overload. Hypertrophy fully developed 2 weeks after AoB. At 4 and 6 weeks, the lung and heart to body weight ratio (LW/BW), a sensitive long-term marker for pulmonary congestion, dramatically increased despite preserved fractional shortening, indicating diastolic dysfunction. The time course of LW/BW was well reflected by E/D, by the ratio of early to late transmural diastolic velocity (E/A) and the deceleration time of E (DT) but not by E/Ea. In agreement, the best correlation with LW/BW was found for E/D (r=0.76; p<0.001), followed by E/A (r=0.68; p<0.001) and DT (r=0.62; p<0.001) whereas E/Ea showed the worst correlation (r<0.51; p<0.001). Furthermore, analysis of receiver-operating characteristic curves for the prediction of increased LW/BW revealed a significantly lower area under the curve for E/Ea (AUC=0.82) compared to those of E/D (AUC=0.98) and DT (AUC=0.95).

Conclusion: E/D but not the mostly preferred index E/Ea reliably detects and monitors diastolic dysfunction in pressure overload. The results may explain previous contradictions regarding the usefulness of E/Ea and suggest advanced validation of the new parameter E/D in humans.
Diagnostic value of exercise E/E' ratio for the early detection of diastolic heart failure in non-obstructive HCM patients
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Background: Heart failure in patients with diastolic dysfunction has a 25% five year mortality rate. It is likely that early detecting patients with diastolic abnormalities will lead to favorable prognosis and survival. Recently, studies on Tissue Doppler Imaging (TDI) have found that the ratio of the peak early diastolic velocity of mitral annulus (E/E') has good correlations with diastolic function. It is still unclear how the indices of diastolic function will change for those non-obstructive hypertrophic cardiomyopathy (HCM) patients. The objective of this study was to test the diagnostic value of exercise E/E' ratio for the early detection of diastolic heart failure (DHF) in non-obstructive HCM patients.

Methods: Echocardiography was performed in 54 non-obstructive HCM patients with normal LVEF and 61 controls before and after exercising after cardiopulmonary exercise testing (CPET). According to the level of E/E' ratio, the patients were divided into the following subgroups: group a, E/E' ratio > 10 both before and after exercise; group b(early DHF), E/E' ratio > 10 before exercise but ≤ 10 after exercise; group c(late DHF), E/E' ratio ≤ 10 both before and after exercise.

Results: (1) The E/E' ratio of patients elevated after exercise (P < 0.01), but that of the controls didn't. (2) The VE/VO2 slope of the patients (28.8 ± 6.4) was higher than that of the controls (26.9 ± 7.7) (P < 0.001). The VO2max of the patients was lower (24.3 ± 5.2) than that of the controls (27.6 ± 3.9) (P < 0.01). (3) In the patients, exercising E/E' ratio had good correlations with exercising S' lateral, exercising E'/E' ratio, and VE/VO2 slope (r = 0.05–0.41). (4) About 1/5 of the patients were found to be early DHF.

E/E' ratios of HCM patients and controls

HCM patients (n=54) Controls (n=61) P value
Post E/E' 8.6±2.5 6.5±1.5 <0.01
Exercising E/E' 9.1±3.0 7.1±1.3 <0.01
P value <0.01 0.085

Conclusions: Exercising E/E' ratio can detect early DHF in non-obstructive HCM patients. Those patients with early DHF have no obvious symptoms and this part of patients should be paid more attention to so as to improve their prognosis.

Presence of preoperative diastolic dysfunction predicts postoperative pulmonary edema in patients undergoing major noncardiac surgery
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Purpose: Patients with left ventricular (LV) diastolic dysfunction are vulnerable to develop pulmonary edema. But the clinical implications of diastolic dysfunction has not been clearly elucidated in patients who underwent major noncardiac surgery. The aim of this study was to evaluate the impact of LV diastolic dysfunction for predicting postoperative (OP) pulmonary edema. Those patients with early DHF have no obvious symptoms and this part of patients should be paid more attention to so as to improve their prognosis.

Methods: 708 patients, older than 60 years (M/F=367/341, Mean age:72±6.7) who underwent transsthorascic echocardiography (TTE) before elective noncardiac surgery were prospectively enrolled. Medical history and TTE variables (LV ejection fraction, LV mass index, LV end-systolic diameter, left ventricular diastolic dimension, age, gender, peak TnI, and pre-MI, e' remained a significant independent predictor of the combined endpoint with a hazard ratio (HR) of 1.18 (1.01-1.39) per 1 cm/s decrease (p=0.045). Patients who had values of both e' and a' below the median, had more than double the risk of an adverse outcome than patients with both e' and a' above the median. (See Table).

Conclusion: The diastolic tissue Doppler velocities seem superior to the conventional echocardiographic diastolic parameters in terms of predicting prognosis after pPCI for patients with STEMI. The early and late diastolic tissue velocities should be evaluated together as they interact on prognosis.

Diastolic tissue doppler velocities predicts adverse outcome after st-elevation myocardial infarction treated with primary percutaneous coronary intervention
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Purpose: To investigate which diastolic echocardiographic parameters that best predict prognosis after an ST-elevation myocardial infarction (STEMI).

Method: From September 2006 to December 2008, 911 patients were admitted with a STEMI, treated with primary Percutaneous Coronary Intervention (pPCI). All patients were examined by echocardiography 1-5 days after the STEMI (median 2 days, IQR 1-3). In total 26 patients were excluded, 14 due to atrial fibrillation and 12 due to inadequate quality of the echocardiographic examination. Treatment effect was assessed in relation to death (n = 29), hospitalization with clinical signs of heart failure (CHF, n = 48) and re-MI (n = 25). Follow-up time was median 19.3 months (IQR 19-39 months)

Results: The diastolic color tissue Doppler velocities, global e' and a', were the only diastolic parameters that remained as independent predictors of the combined outcome (Death, CHF, and re-MI) in a multivariable Cox regression analysis using forward selection including all diastolic parameters and age, previous myocardial infarction (pre-MI) and peak troponins (Tnl). Even after adjusting for exercise fraction, left ventricular mass index, left ventricular diastolic dimension, age, gender, peak TnI, and pre-MI, e' remained a significant independent predictor of the combined endpoint with a hazard ratio (HR) of 1.18 (1.01-1.39) per 1 cm/s decrease (p=0.045). Patients who had values of both e' and a' below the median, had more than double the risk of an adverse outcome than patients with both e' and a' above the median. (See Table).

Conclusion: Clinicians need to be cautious on intravenous fluid therapy for surgical patients with findings of high E/E' ratio, E/A ratio, LVMI in TTE.
Exercise left ventricular filling pressure: prognostic implications in patients after acute myocardial infarction

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Purpose: To evaluate the prognostic value of exercise left ventricular filling pressure to outcomes in patients (pts) after acute myocardial infarction.

Methods: 83 pts (68 men; mean age 57 years); 13±3 days after acute myocardial infarction were studied. In all pts left ventricular filling pressure was estimated from the ratio of transmural and annular velocities (E/E') at rest and after bicycle exercise (25W, 3-min increments). Patients were classified according to E/E' ratio at rest: 48 had E/E' <10 (Group I) and 35 had E/E' >10 (Group II). Patients were followed for cardiovascular hospitalization and death for 24 months.

Results: Of 83 pts exercise E/E' rose in 23 (27.7%) pts: for Group I in 11 pts (from 3.7±0.75 to 9.4±1.1, p<0.005; difference 18.9%), and for Group II in 12 pts (from 11.5±0.9 to 14.0±1.3, p<0.001; difference 21.7%). Exercise duration was significantly shorter in pts with than in pts without raised exercise E/E' (p<0.025). During follow-up period, there were 19 cardiovascular hospitalization (8 in pts with and 11 in pts with exercise increased E/E'; 13.9%, vs 47.8%) and one cardiovascular death (in Group II in patient with exercise increased E/E'). The incidence of hospitalization among pts with pts exercise increased E/E' was higher in Group II (7/12pts, 58.3%), than in Group I (4/11pts, 36.4%).

Conclusion: Raised exercise left ventricular filling pressure in patients after acute myocardial infarction is associated with higher rate of subsequent cardiovascular hospitalization and death.

Systolic and diastolic function

Table 1. CHF parameters and BNP levels in middle-aged patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total, n=38</th>
<th>CFIR &gt;1.77, n=19</th>
<th>CFIR &gt;1.77, n=19</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF %</td>
<td>31 (26.3±3.5)</td>
<td>29.5 (25.34)</td>
<td>31.5 (27.33)</td>
<td>0.35</td>
</tr>
<tr>
<td>E/A</td>
<td>0.9±(0.7-1.5)</td>
<td>0.3 (0.2-0.8)</td>
<td>0.7 (0.6-1)</td>
<td>0.003</td>
</tr>
<tr>
<td>E'</td>
<td>12.5±(8.9-18.0)</td>
<td>16.4 (11.6-25.0)</td>
<td>9.3 (8.3-20.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>200±(160-240)</td>
<td>180 (140-220)</td>
<td>218 (170-270)</td>
<td>0.02</td>
</tr>
<tr>
<td>IRT (ms)</td>
<td>100±(80-115)</td>
<td>80 (60-100)</td>
<td>100 (100-120)</td>
<td>0.004</td>
</tr>
<tr>
<td>Atrial volume index (m²/m²)</td>
<td>40.4 (25.5-45.4)</td>
<td>47.1 (40.58-58.8)</td>
<td>27.9 (19.4-41.9)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

LVEF: left ventricular ejection fraction; E: early mitral inflow velocity; A: late mitral inflow velocity; E': early tissue Doppler velocity; IRT: isovolumetric relaxation time.

Conclusion: The E/E' index by TDI in patients with PLVEF may be a helpful tool for evaluating aortic stiffness, cardiac afterload and diastolic LV function.

Association between Eas index by tissue Doppler imaging and ventricular stiffness index or ventriculoarterial interaction in patients with preserved left ventricular ejection fraction

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Purpose: Left ventricular (LV) stiffness contributes to cardiac afterload, LV hypertrophy and substrate of cardiac function. We previously reported that Eas index of diastolic and systolic performance: e'/a' (s). We also examined LV-diastolic elastance index (Ed), arterial elastance index (Ea), LV end-systolic elastance index (Ees), ventricular-vascular coupling index (10-Ea/Ees) and total stiffness index (10-Ed/Ea/Ees). Furthermore, we investigated the relation between plasma troponin (ln-h) - brain natriuretic peptide (BNP) levels and LV stiffness parameters.

Results: The Eas index was significantly and negatively correlated with Ed (r=-0.466, p=0.0001), Ea (r=-0.180, p=0.0002), ventricular-vascular coupling index (r=-0.117, p=0.016), total stiffness index (r=0.281, p=0.0001) and plasma In-BNP levels (r=-0.333, p=0.0001). However, Eas was not associated with Eas index. Finally, multivariate logistic regression analysis showed that plasma In-BNP levels were most closely correlated with Ed (p=0.0001).

Conclusion: The Eas index by TDI in patients with PLVEF may be a helpful tool for evaluating aortic stiffness, cardiac afterload and diastolic LV function.

Mycardial function “diastology” / Myocardial function “Ischemic cardiomyopathy”

P4244

Stress-echocardiography to identify restenosis in drug eluting stent patients

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Purpose: Restenosis is defined “Achilles Heel” of percutaneous cardiac inter-
End-systolic pressure-volume relation and ventricular-arterial coupling predict cardiac events in patients with negative stress echocardiography

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Background: A maximal negative stress echo identifies a low risk subset for coronary events. However, the potentially prognostically relevant information on cardiovascular hemodynamics for heart failure-related events is unsettled. Aim To assess the prognostic value of stress-induced variation in cardiovascular hemodynamics in patients with negative stress echocardiography.

Methods: We enrolled 929 patients (618 males; mean age 63±12; ejection fraction 48±17%, Wall Motion Score Index = 1.48±0.63, ischemic dilated cardiomyopathy, n = 109; dilated cardiomyopathy, n = 222; valvular, n = 90, known or suspected coronary artery disease, n = 508), with negative (exercise 238, diprydiamol 190) stress echocardiography result. Cardiovascular hemodynamics were assessed during stress: end-systolic pressure/volume ratio (ESPVR); ventricular arterial coupling (VAC) indexed by the ratio of the ESPVR to arterial elastance (Es, ratio of end-systolic pressure by stroke volume). Cardiac output (CO, stroke volume x heart rate) calculated at baseline and at peak stress.

Results: During a median follow-up of 16 months (interquartile range 6-32), 52 deaths and 94 hospitalization occurred. Receiver-operating-characteristic curves, and the corresponding areas under the curve, show the predictor performance of hemodynamic changes during stress (Δ ESPVR, Δ VAC, Δ Es and Δ CO) in the EX, DIP and DOB subsets (Figure, Panel A, B, C).

Conclusion: Patients with negative stress echocardiography may experience an adverse outcome, which can be identified by Δ ESPVR and Δ VAC.

Feasibility, symptoms, adverse effects and complications associated with non invasive assessment of coronary flow velocity in women with suspected or known coronary artery disease.

Experience in 1455

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Purpose: Noninvasive assessment of coronary flow velocity reserve (CFVR) with transthoracic echocardiography (TTE) is an increasingly used method to evaluate the effects of epicardial coronary stenosis and coronary microvascular dysfunction. The purpose of this investigation was to analyze and review the Cagliari University experience in assessing CFVR with TTE to define the feasibility, safety, adverse event profile, and complications rate of the test in women with and suspected coronary artery disease (CAD).

Methods: We evaluated CFVR in the left anterior descending coronary artery (LAD) with TTE during adenosine infusion. The pulsed wave Doppler of blood flow velocity was recorded in the LAD at rest and after maximum vasodilation by adenosine infusion (140 mcg/kg/min in 5 minutes). We analyzed 1455 consecutive CFVR TTE studies starting from January 2000 to December 2010. The patients (age: 66.4±11.9 years; mean 14.89 years) were referred for CFVR studies for different reasons: 933 (64.1%) for programed follow up after elective and primary PTCA on LAD, 370 (25.4%) for angina, 11 (0.8%) for hypertrophic cardiomyopathy, 38 (2.6%) for hypercholesterolemia, 77 (5.3%) for systemic scle-rosis, 25 (1.7%) for others reasons.

Results: A complete CFVR study was achieved in 1429 pts (feasibility: 99.6%), the test being performed also in the early phase of acute coronary syn- drome and in obese women. In the remaining 26 patients (1.8%) the study was interrupted because of hyperpnea (8), general malaise (8), failure to visualize LAD (2), chest pain without EKG changes (2), nausea and headache (2), chest pain with ischemic EKG (1), hypertensive status (systolic blood pressure 200 mmHg, 1), hypotension (70/50 mHg, 1), caffeine assumption (1).

Minor symptoms or adverse effects occurred in 548 pts (38.3%) not requiring test termination: hyperepnea (239,16.7%), flushing (134,9.4%), chest pain without EKG changes (7%), headache (95.6,3%), minor arrhythmias (3.5%), chest pain with EKG changes (1.5%). No major complications were observed during all studies.

Conclusion: Non invasive assessment of CFVR in LAD by TTE is a very feasible method with very low incidence of adverse events and complications in women with suspected or known CAD. It can be used and safely performed in the evaluation of women with atherosclerotic LAD disease and in a broad spectrum of cardiac disease with microvascular impairment.

Gender difference of diagnostic utility ofdobutamine stress echocardiography with early atropine administration in detection of coronary artery disease

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Background: Lower diagnostic accuracy of electrocardiographic exercise test in female patients is well-known from numerous metaanalysis and echocardiographic stress tests were proposed especially for women to improve detection of coronary artery disease (CAD).

Aim: Our aim was to compare sensitivity, specificity, predictive values and accuracy of significant coronary artery stenosis detection between men and women undergoing dobutamine-atropan stress echocardiography (DASE).

Methods: 238 patients (105 women and 133 men, mean age 62±9, 28% with history of myocardial infarction) with chest pain or other symptoms suggesting coronary artery disease were enrolled. We defined as positive stress echocardiography test termination: hyperpnea (239,16.7%), flushing (134,9.4%), chest pain without EKG changes (7%), headache (95.6,3%), minor arrhythmias (3.5%), chest pain with EKG changes (1.5%). No major complications were observed during all studies.

Results: In female group, mean age 62±10±3, 37 (35%) had significant CAD and 19 (51% of CAD) 1VD (one vascular disease), in male group, mean age 61,7±8,9, 90 (68%) had CAD and 44 (49% CAD) 1VD. Percentage of MI was higher in men: 44±4% vs 12±4%, p<0.0001. All included to analysis test were diagnostic.

Conclusions: In women presented with a higher diagnostic utility than in men as confirmed by comparison of areas under independent ROC curves curves AUC=0.878 in women (standard error=0.03) and 0.734 in men (SE= 0.0415) with p value for this comparison <0.0057. Also for 1VD diagnostic value of DASE was significantly higher in women. Detailed diagnostic values are displayed in table.

Diagnostic efficacy of DASE

<table>
<thead>
<tr>
<th>Sex</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>85.6</td>
<td>60.5</td>
<td>81.9</td>
<td>66.7</td>
<td>77.5</td>
</tr>
<tr>
<td>Women</td>
<td>91.9</td>
<td>83.8</td>
<td>95</td>
<td>75.6</td>
<td>86.7</td>
</tr>
<tr>
<td>Men 1VD</td>
<td>81.8</td>
<td>40.5</td>
<td>76.5</td>
<td>67.9</td>
<td>71.3</td>
</tr>
<tr>
<td>Women 1VD</td>
<td>94.7</td>
<td>89.8</td>
<td>95.2</td>
<td>86.2</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Contrary to ECG exercise test, DASE with early atropine injection seems to offer higher diagnostic potential for accurate detection of significant coronary stenosis in women than in men especially in 1VD.

Coronary flow velocity reserve in 3 major coronary arteries can be a promising alternative for fractional flow reserve in determining hemodynamic significance of coronary artery disease

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Objective: To evaluate whether coronary flow velocity reserve (CFVR) in 3 ma-jor coronary arteries by transthoracic echocardiography can be a counterpart of...
fractional flow reserve (FFR) in assessing hemodynamic significance of coronary artery disease (CAD).

Methods: This is a prospective study in 157 vessels of 142 patients with suspected coronary artery disease. Three-dimensional intravascular ultrasound for suspected CAD. Carotid plaque, not clinical risk factors, is associated with higher prevalence of carotid disease compared to Ranolazine improves coronary flow reserve in Left ventricular torsion during exercise in patients and at PK, were lower in G-LAD (8.8 ± 0.05; 58.13 ± 71.10, p < 0.001). E/e' values were similar (11.4 ± 4.0 vs. 13.7 ± 71.11, R = 1, 55.5 ± 51.2 ± 7.2 at PK). Tor was lower at R and PK in G-LAD. The decreased PK-Tor was partly explained by increased basal rotation. The ± of T or and % of T or were lower for Tor correlated weakly with LVEF (Tor and LVEF at R, r = 0.33, p < 0.001; Tor and LVEF at PK, r = 0.13, p = 0.01) and did not with E/e' (R or PK).

P4249
Higher prevalence of carotid disease compared to myocardial ischaemia in patients undergoing simultaneous stress echocardiography for suspected coronary artery disease
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Background: Presence of carotid artery disease (increased carotid intima-media thickness (C-IMT) >75th percentile for age and sex) and/or presence of plaque in accordance with Mannheim consensus. FRS was also assessed. Patients underwent coronary angiography based on clinical grounds and SE data. Results: Of the 262 consecutive patients (128 male (49%), mean age 60.0 ± 11 years), 36 (14%) demonstrated myocardial ischemia by SE, of which the majority (26 patients (72%)) had coronary disease. These consisted of 18 patients (50%) with carotid plaque and 13 (36%) with C-IMT >75th percentile. However, coronary disease was also present in 137 of 208 (61%) with normal SE, plaque was demonstrated in 96 (43%) and C-IMT >75th percentile in 91 (40%). FRS was significantly higher (p < 0.001) in patients with carotid disease (19.0 ± 6.5 vs. 7.87). However, coronary disease was also present in 72 (51%) and 44 (31%) of patients in low-intermediate FRS and normal SE, 37 patients of the total 262 underwent coronary angiography, of which 28 (75%) demonstrated CAD. Subsequently, 13 (45%) underwent revascularization (median: 1 month). Plaque showed significant association with CAD (p = 0.002) and revascularization (p = 0.012), even after adjustment for all known coronary risk factors and FRS.

Conclusions: There is a significantly higher prevalence of carotid disease compared to myocardial ischemia in patients undergoing simultaneous SE and carotid ultrasound for suspected CAD. Carotid plaque, not clinical risk factors, is associated with higher prevalence of carotid disease compared to myocardial ischemia in patients undergoing simultaneous stress echocardiography for suspected coronary artery disease.

P4251
Abnormal stress echocardiography in the presence of normal stress echocardiography
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Background: Previous studies are contradictory with regard to proving that patients with ischemic changes in the electrocardiogram (ECG) but normal wall motion contractility during a stress echocardiography (SE) study have a worse prognosis than those in whom both the ECG and wall motion contractility are normal during SE. The aim of the present study is to assess the cardiac outcome of patients who underwent SE and compare the cardiac outcome among patients with and without ECG change during a normal stress SE study.

Methods: This is an observational study performed on 3,322 patients who underwent SE from January, 2007 through the end of December, 2010. The primary endpoint was a composite of all-cause mortality and acute MI. According to SE results, the patients were stratified into three groups: group I: normal SE and normal stress ECG (n = 2,107); group II: normal SE and abnormal stress ECG (n = 868), and group III: abnormal SE (n = 347).

Results: Patients in group III were older than patients in groups I and II (67±10 years and 57±12, respectively) and was comprised of a higher ratio of male patients (71% in group III, 59% in groups I and II). Group III patients had a significantly higher prevalence of diabetes (13% vs. 8%), dyslipidemia (34% vs. 22%), and hypertension (28% vs. 17%) than patients in groups I and II. In multivariate Cox proportional regression analysis with adjustment for baseline demographics and comorbidities, no difference was found in the outcome of patients in groups I (reference group) and II (hazard ratio 0.18, 95% CI 0.69-2.24). An abnormal SE was a significant factor impacting survival, and increased the risk of MI and/or death by 2.11 (95% CI 1.16-3.81, p = 0.014).

Conclusion: The negative predictive value for MI and/or death of a patient with normal SE is extremely high. Our study proves that there is no difference in the cardiac outcome of patients with ischemic changes in the ECG during SE and those with normal ECG during a stress echocardiography study.

P4252
Ranolazine improves coronary flow reserve in patients with angina but no obstructive coronary artery disease
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Background: Ranolazine reduces the Na-dependent cardiac sodium load via inhibition of the late sodium current, improving diastolic tone and oxygen handling during myocardial ischemia. In patients with angina, evidence of myocardial ischemia, but no obstructive coronary artery disease (CAD), microvascular coronary dysfunction plays a key role. Transhoracic Doppler-derived coronary flow reserve (CFR) is known as an index of coronary arterial reactivity and decreases under the condition with microvascular dysfunction as well as coronary artery stenosis.

The aim of this study was to assess the effect of ranolazine on CFR in this patient group.

Methods: 52 patients (36 M, 16 F; mean age 63±10 years) with angina and evidence of microvascular CAD, but no obstructive CAD, was enrolled in a double-blind, placebo-controlled trial. All of them underwent coronary angiography, to exclude obstructive CAD, and catheterization was performed by the femoral approach after local anesthesia induced with 0.5% lidocaine.

Conclusion: In conclusion, Tor at R and at PK are decreased in pts with ISD in the LAD territory, but the ± in Tor is similar to that of pts with normal ExE.
Dipyridamole coronary flow reserve stratifies prognosis in patients without left anterior descending artery disease following an acute coronary syndrome

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Background: Coronary flow reserve (CFR) assessment by transthoracic ultrasound of the left anterior descending artery (LAD) during dipyridamole echocardiography has been shown to predict prognosis in large unselected populations, and to be correlated with significant stenosis of the LAD. The aim of the present study was to assess the prognostic impact of CFR in subjects with acute coronary syndrome and proven absence of LAD disease.

Methods: 325 patients with ACS underwent high-dose dipyridamole stress with combined assessment of CFR in the LAD and wall motion analysis, followed by coronary angiography. 152 patients without LAD disease (stenosis >50%) and with interpretable CFR recordings were monitored for major adverse cardiac events (MACE) for a mean of 30 months.

Results: 22 patients developed events during follow-up. Patients who experienced MACE differed from stable patients in terms of age, prevalence of diabetes, number of diseased vessels and CFR values. Multiple logistic regression analysis for the prediction of MACE demonstrated independent value only for CFR (p < 0.001), smoking (p < 0.01) and age (p < 0.05). ROC curve analysis showed that a CFR < 2.5 is able to predict MACE with a sensitivity of 86.4% and a specificity of 80% (AUC = 0.86).

Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>65 ± 11</th>
<th>58 ± 10</th>
<th>&lt; 0.005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>165</td>
<td>90/34</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetic (n)</td>
<td>8 (37%)</td>
<td>17 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoke (n)</td>
<td>14 (64%)</td>
<td>59 (46%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>4 (19%)</td>
<td>23 (18%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia (n)</td>
<td>14 (64%)</td>
<td>59 (46%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertriglyceridemia (n)</td>
<td>3 (16%)</td>
<td>17 (13%)</td>
<td>NS</td>
</tr>
<tr>
<td>WMSI</td>
<td>1.73 ± 0.18</td>
<td>1.17 ± 0.28</td>
<td>NS</td>
</tr>
<tr>
<td>0.1/2 vessel CAD (n)</td>
<td>1/14/7</td>
<td>47/71/19</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CFR</td>
<td>2.11 ± 0.33</td>
<td>2.58 ± 0.44</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Conclusions: In a population of patients with ACS, CFR significantly improves prediction of MACE when added to standard clinical variables, even in the absence of LAD disease. This finding promotes the role of ultrasound-assessed CFR in the risk stratification after ACS, supporting the concept that CFR reflects global atherosclerotic burden, endothelial dysfunction and microvascular damage, more than just mirroring focal LAD disease.

Left ventricular torsion at rest, peak and post-exercise echocardiography

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Left ventricular torsion (Tor) has not been widely studied during exercise echocardiography (ExE). We aimed to study the feasibility of the assessment of ExE during ExE and the likely correlations with systolic and diastolic function.

Methods: A series of 265 consecutive patients referred for ExE were studied by transthoracic imaging at rest (R), peak (P), and within 1 min post-ExE (PEx). ExE were performed in 214 patients at R (81%), in 193 at P (73%) and in 179 within 1 min of the cessation of the exercise (68%). Apical rotation, twist and Tor increased during exercise, whereas basal rotation was similar. All rotation parameters but basal rotation were significantly different at P and PEx. Significant correlations were found between rotation parameters and LVEF at R (LVEF and apical rotation, r = 0.39; LVEF and twist, r = 0.35; LVEF and Tor, r = 0.38; all p < 0.001) and at PEx (LVEF and apical rotation, r = 0.16, p = 0.02; LVEF and twist, r = 0.28, p < 0.001; LVEF and Tor, r = 0.28, p < 0.001). However these parameters did not correlate with ExE values.

In conclusion, rotation can be assessed during exercise in about 70% of the cases. PEx exercise rotation parameters are significantly different to those obtained at R and P.

Estimation of infarct size using transthoracic measurement of coronary flow reserve in infarct related and reference coronary artery


Purpose: To assess the feasibility and clinical utility of transthoracic measurement of coronary flow reserve (CFR) in patients with acute myocardial infarction (AMI) and to estimate the size of infarct using CFR.

Methods: We prospectively enrolled 43 patients with AMI. CFR was assessed using dipyridamole stress echocardiography in the infarct related artery and the reference coronary artery. Invasive CFR was also measured at the time of diagnostic coronary angiography. CFR was measured in the infarct related artery, distal normal and proximal normal segments of the reference coronary artery. CFR was measured in segments of the reference coronary artery proximally, distally and at the infarct related artery. CFR was assessed using echocardiographic angiography and color Doppler flowmetry. CFR was calculated as the ratio of hyperemic coronary blood flow to baseline coronary blood flow. CFR was determined as the ratio of hyperemic, induced by intravenous dipyridamole administration, to baseline diastolic coronary flow velocity. CFR was assessed before and after 8-weeks therapy.

Results: There were no significant differences in baseline characteristics between Ranolazine and placebo group. CFR was successfully performed in all patients. Baseline CFR was not significantly different in Ranolazine and placebo group (1.85 ± 0.27 vs. 1.87 ± 0.29 – p = 0.98). After 8 weeks CFR significantly increased in Ranolazine group (2.02 ± 0.18 vs. 1.85 ± 0.27 – p = 0.007) but not in placebo group (1.90 ± 0.24 vs. 1.87 ± 0.29 – p = 0.98). No patient dropped out during 8 weeks therapy. Side effects were similar in both groups.

Conclusions: In patients with evidence of microvascular ischemia, but no obstructive CAD, Ranolazine is able to improve CFR. This is probably due to improvement in microvascular coronary dysfunction. Larger studies will be able to confirm these data.

Incorporation of myocardial contrast echocardiography into a clinical stress echocardiography service is feasible and provides additional diagnostic information

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Purpose: A large evidence base supports the diagnostic accuracy of myocardial contrast echocardiography (MCE), performed during stress echocardiography (SE), for the detection of myocardial ischaemia and viability in patients with known or suspected coronary artery disease. However, the feasibility and value of MCE incorporated into a clinical SE service in a real-world setting is unknown. We therefore performed this study to establish the role of MCE in the clinical arena.

Methods: All patients had been referred for SE on clinical grounds. Patients with known allergy to sulphur-containing drugs or referred for non-ischaemic studies (e.g. valve disease or HOCM) were excluded. We performed MCE during SE – using a continuous intravenous infusion of Sonovue contrast – in all patients undergoing pharmacological stress and patients undergoing treadmill exercise in whom we suspected a high workload or target heart rate may not be attained. We documented prospectively demographic variables, reasons for referral, stress modality, number of contrast vials used and value of MCE, which was assigned to one of four pre-determined categories: incremental benefit over wall motion (WM) analysis, more confidence with WM analysis, no benefit over WM analysis or other (i.e. uninterpretable MCE images). All MCE studies were analysed by the performing cardiologist together with an expert reader.

Results: Over a 13 month period, 544 patients underwent SE and 142 (26%) of these also underwent MCE by different operators. Mean age was 63yrs (range 19-89); 77% were male. MCE demonstrated excellent feasibility, with diagnostic perfusion images obtained in 95% studies. Mean contrast use was 2.9 vials per study. MCE data provided the interpreting cardiologists with incremental benefit over WM analysis in 40 (28%) cases, gave greater confidence with WM analysis in 28 (20%) cases, had no added value over WM analysis in 67 (47%) cases and was uninterpretable in 7 (5%) cases. Mean number of segments with indiscernible ischaemia was 2.8±0.27 by WM and 5.6±0.28 by perfusion (p<0.001). Of the 52/142 patients that also underwent angiography, perfusion data agreed with angiographic findings in 45 (81%) cases. Agreement between MCE and angiography findings were 18/21 (86%) and 14/16 (88%) in those in whom MCE data was of incremental benefit and added confidence, respectively.

Conclusion: MCE is feasible by multiple operators when incorporated into a clinical SE service. MCE data is either of incremental benefit over WM analysis or gives more confidence with WM analysis in a significant proportion (approximately 50%) of cases.
Prediction of left ventricular function recovery with pharmacologic agent low-dose dobutamine stress echocardiography for the prediction of functional recovery 12 months after STEMI.

Transmural strain parameters assessed by 2D speckle tracking predicting functional recovery 12 months after STEMI. 85.2%. Transverse parameters of strain had nonsatisfactory diagnostic value for graphy in the study group was 75.8%, with sensitivity of 61.8%, and specificity of -10.1%, while diagnostic accuracy for low-dose dobutamine stress echocardiography was defined as >70% diameter reduction. CFR was determined as ratio between the peak diastolic flow velocity during adenosine infusion and at baseline condition, a cutoff value for significant stenosis was -2.

Results: There was a good correlation (r=0.56, p<0.001) between morphological changes detected with ICA and functional parameters of stenosis determined by CFR and a considerable correlation between invasive and noninvasive coronary angiography (r=0.57, p<0.001). A much weaker correlation was between MSCT angiography and CFR (r=-0.22, p=0.086).

MSCT had sensitivity 86.2%, specificity 69.1%, positive predictive value 59.5%, negative predictive value 90.5% and accuracy of 75.5% in detection of significant RCA stenosis. CFR had sensitivity 76.9%, specificity 85.3%, positive and negative predictive value 82.9% and accuracy 81.7. When the results of both methods were agreed accuracy was improved to 90.0%, specificity 76.9%, specificity 100.0%, positive 100.0% and negative predictive value 85.0%.

ROC curve estimation of MSCT angiography in detection of significant RCA stenosis (Area 0.81, p<0.001) for diameter of stenosis of 67.5% had a sensitivity 86.0% and specificity 63.6%, ROC curve of CFR (Area 0.84, p<0.001) for CFR >0.2 had a sensitivity 76.9% and specificity 68.6%. Comparing ROC curves there was no statistical difference (p=0.747).

Conclusion: CFR determined by TDE had an additive diagnostic value in evaluation of real significance of atherosclerotic lesions on RCA detected with MSCT angiography, what emphasize importance of comprehensive noninvasive imaging approach integrating morphologic and functional information.

P4258
Prediction of left ventricular function recovery with the use of 2D speckle tracking echocardiography in patients 12 months after acute ST-elevation myocardial infarction E. Szymczyk, P. Lipiec, B. Michalski, K. Szymczyk, Ł. Stefanczyk, B. Wozniakowski, A. Rotkiewicz, J.D. Kasprzak, Medical University of Lodz, Lodz, Poland

Introduction: Prediction of left ventricular function recovery is of clinical importance for the management and prognosis of patients after myocardial infarction. The aim of this study was to assess if the use of 2D speckle tracking in resting echocardiography may be helpful in the prediction of left ventricular function recovery in patients 12 months after ST-elevation myocardial infarction (STEMI). Material and methods: The study group consisted of 96 patients (69 male, mean age 58±10 years) with first STEMI treated with successful primary percutaneous coronary intervention. 7-12 days after STEMI, all patients underwent resting echocardiography. All acquired images were analyzed off-line using 2D speckle tracking technique. Measurements included peak systolic longitudinal and transverse strain (SLS and STS), peak longitudinal and transverse strain (PLS and PTS) including possible postischemic shortening, systolic longitudinal and transverse strain rate (SLSR and STSR) at baseline (rest). After 12 months each patient underwent control resting echocardiography with visual assessment of functional recovery in akinetic/dyskinetic segment as defined as improvement from dyskinesis and akinesis to hypokinesis or normokinesis.

Results: At baseline there were 265 segments with akinesis or dyskinesia. 112 (42%) of those segments showed functional recovery after 12 months. Longitudinal strain parameters SLS (AUC=0.710, p=0.001) and PLS (AUC=0.773, p=0.001) had good, while SLSR only satisfactory (AUC=0.648, p=0.001) diagnostic value for predicting functional recovery. The highest prognostic value of 72.9% was for PLS < -10.4% and of 67.5% for SLS < -10.1%, while diagnostic accuracy for low-dose dobutamine stress echocardiography in the study group was 75.8%, with sensitivity of 61.8%, and specificity of 85.2%. Transverse parameters of strain had non-satisfactory diagnostic value for predicting functional recovery 12 months after STEMI.

Conclusions: Longitudinal strain parameters assessed by 2D speckle tracking had comparable prognostic value to requiring experience and administration of pharmacological agent low-dose dobutamine stress echocardiography for the prediction of left ventricular functional recovery in patients 12 months after STEMI. The proposed method may be less dependent on subjective factors and inherent in usual viability interpretation based on dobutamine stress echocardiography and offer a methodological background for fully computerized algorithms.

P4259
QRS fragmentation in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy and complete right bundle branch block S. Peters, St. Antonius-Hospital Gronau GmbH, Gronau, Germany

Patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy ARVD/C and complete right bundle branch block (RBVB) very often have recurrent ventricular tachycardia and develop biventricular heart failure in the follow-up requiring heart transplantation and/or diuretics. In other patients with ARVD/C excluding right bundle branch block QRS fragmentation in the S wave of right precordial leads identifies patients with recurrent VT, primary VF and recurrent ICD discharges; QRS fragmentation ≥ 3 leads characterised patients who died from sudden cardiac death.

Method: Among a total of 374 patients with ARVD/C (208 males; mean age 46.5±14.8 years) there were 22 patients with complete RBVB. 17 patients with ARVD/C developed complete right bundle branch block and had biventricular heart failure. In 6 patients with ARVD/C excluding right bundle branch block an initial QRS fragmentation ≥ 3 of all 12 ECG leads was observed. In 5 patients with complete right bundle branch block were initially evident. In all patients with ARVD/C and RBVB QRS fragmentation ≥ 3 of all 12 ECG leads and QRS fragmentation in the S wave of right precordial leads were analysed.

Results: QRS fragmentation ≥ 3 of all 12 ECG leads and in the S wave of right precordial leads were present in 16/17 patients who developed RBVB and none of the 5 patients with initial RBVB QRS fragmentation ≥ 3 leads was present (n=12.5; p<0.001).

Conclusion: Patients with recurrent ventricular tachycardia who develop biventricular heart failure requiring heart transplantation and/or diuretics are characterised by QRS fragmentation in the S wave of right precordial leads ≥ 3 of all 12 ECG leads. These results are statistically significant. Patients with initial RBVB have an overall benign prognosis.

P4260

Purpose: This case-control study was conducted to evaluate the interrelation between the occurrence of heart failure (HF) and the sleep apnea in the patients with hypertrophic cardiomyopathy (HCM) excluding obstructive left-ventricular outflow tract stenosis (LVO).

Methods: 48 patients with apical HCM, mid-ventricular HCM, and non-obstructive left-ventricular outflow tract HCM were included. Polysomnography was used to measure the apnea-hypopnea index (AHI). The biomarkers and cytokines including brain-natriuretic peptide (BNP), plasma renin activity, aldosterone, adrenaline, nor-
adrenalin, dopamine, soluble tumor necrosis factor receptor 1 (sTNFR1), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), transforming growth factor-beta (TGF-beta1), urine 8-hydroxydeoxyguanosine (8-OHdG) were measured at the period of HF decompensation. We divided those patients into two groups with (n=14) or without (n=34) a history of HF requiring hospitalization and compared above-mentioned parameters between two groups.

**Results:** HCM patients with a history of HF has significantly higher AH1 (32±5.0 vs. 11.1±2.2, p<0.0001) and higher TGF-beta1 value (2.7±2.49 vs. 1.5±0.07, p=0.016) comparing with those without a history of HF. The other indices of HF, inflammation, and oxidative stress, such as BNP, PRA, aldosterone, adrenalin, nor-adrenalin, dopamine, sTNFR1, TNF-α, IL-6, 8-OHdG have not shown any significant difference between two groups.

**Conclusions:** Sleep apnea may play an important role in the occurrence of HF in the patients with relatively benign HCMs. The elevation of TGF-beta1 may suggest the involvement of fibrosis in the pathogenesis of HF in the patients who have both HCM and sleep apnea.

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**Predictors of survival in patients with restrictive cardiomyopathy**

J.Y. Jang1, D.-H. Kang1, B.J. Sun1, M.S. Kim1, D.H. Kim1, J.M. Song1, J.-H. Zo1, K.-J. Choi1, J.-K. Song1, J.-J. Kim1, 1Asan Medical Center, Seoul, Korea Republic of; 2Borame Hospital, Seoul, Korea, Republic of

**Backgrounds:** Restrictive cardiomyopathy (RCMP) is a rare heterogenous disease and the survival according to types of RCMP is unclear. We evaluated clinical outcomes of RCMP to identify predictors of survival.

**Methods:** From 1999 to 2010, we prospectively studied 98 consecutive patients (64 men, age:58±11 years) diagnosed as RCMP. All patients had the symptoms of heart failure and diastolic dysfunction with preserved left ventricular systolic function on echocardiography. Diagnosis of RCMP was initially made by typical echocardiographic findings and confirmed by endomyocardial biopsies. The endpoint was defined as death from any cause.

**Results:** Idiopathic RCMP was diagnosed in 11 (11%) patients, and infiltrative CMP in 87 (89%). The underlying cause of infiltrative CMP was amyloidosis in 56 (64%), idiopathic myocarditis in 77, light-chain deposition disease in 5, myocarditis in 2, hypereosinophilic syndrome in 2, and Fabry disease in 1. During a median follow-up of 6 months (IQR, 0.4-20.4), 34 patients died with a median follow-up of 4 months (IQR, 1-11). The annual mortality rate was 9.2%. Female gender (HR 1.15, CI 95% 1.08-1.22, p<0.001) and restrictive pattern (HR 2.92, CI 95% 1.68-5.11, p=0.001) were independent predictors of death.

**Conclusions:** Idiopathic CMP was the predominant type of RCMP and related with much worse survival. Early diagnosis of RCMP by echocardiography and timely institution of chemotherapy may improve the prognosis of cardiac amyloidosis.

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**Characterization of predictors of in-hospital cardiac complications of takotsubo cardiomyopathy: multi-center registry from Tokyo CCU network**

T. Murakami1, T. Yoshikawa1, Y. Maekawa1, T. Ueda1, T. Isogai2, Y. Konishi1, K. Saita1, K. Nago1, T. Yamamoto1, M. Takayama1 on behalf of Tokyo CCU network Committee. 1Sakakibara Heart Institute, Department of Cardiology, Tokyo, Japan; 2Keio University, Tokyo, Japan; 3Tokyo metropolitan Tama Center, Tokyo, Japan; 4Makuhari Red Cross Hospital, Tokyo, Japan; 5Kyorin University, School of Medicine, Tokyo, Japan; 6Jichi Medical University, Tokyo, Japan; 7Nippon Medical School, Tokyo, Japan

**Background:** Takotsubo cardiomyopathy (TC) is an acute cardiac syndrome characterized by transient left ventricular dysfunction and relatively good prognosis after discharge. However, cardiac complications during hospitalization remain to be fully determined.

**Methods:** We investigated 107 patients of TC (82 women, median age 73.9±11.1 years old) from Tokyo CCU network database, comprising of 67 cardiovascular centers in the metropolitan area during January 1 to December 31 2010. Cardiac complications were defined as all-cause death, pump failure (Killip II/III/IV), sustained ventricular tachycardia (SVT), ventricular fibrillation (VF), and advanced atrioventricular block (AVB). We attempted to characterize cardiac complication groups (CC) by comparing patients with and without cardiac complication (NC) during hospitalization.

**Results:** CC was observed in 41 patients (all-cause death, n=9; pump failure, n=27; SVT, n=1; AVB, n=2; VF, n=2), and there was no complication in the remaining 66 patients. There was no difference in age (75.2±10.4 vs. 72.9±11.6, p=0.289), female gender (70.7% vs. 80.3%; p=0.144), peak creatinine kinase level (IU/l) (553±710 IU/l vs. 486±1024 IU/l, p=0.780), C-reactive protein level (mg/dl) (2.63±3.75 vs. 1.90±4.25 mg/dl, p=0.379) and ST elevation on electrocardiogram (68.3% vs. 75.8%, p=0.389), respectively. White blood cell count (WBC) (11189±4516/ul vs. 9023±3552/ul, p=0.005) and brain natriuretic peptide (BNP) (1125±1245 pg/ml vs.376±764 pg/ml, p=0.004) were higher in CC than NC. Left ventricular ejection fraction was lower in CC than NC (42.3±11.6% vs. 53.1±11.0%, p<0.001).

**Conclusion:** Cardiac complications are not rare in patients with TC during hospitalization. Higher WBC and BNP levels and the presence of LV dysfunction seem to be possible predictors of TC with cardiac complications.

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**Prognostic role of clinical presentation in patients with hypertrophic cardiomyopathy: A single center experience**

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**Background and Aims:** Hypertrophic cardiomyopathy (HCM) is a complex primary and genetically transmitted heart muscle disease characterized by highly variable natural history, from stable clinical course over many years to progressive congestive heart failure (HF) or sudden death (SD). The aim of the study is to evaluate the long-term prognostic impact of baseline symptoms in a cohort of HCM patients.

**Methods and Results:** We considered 212 HCM patients enrolled in the Trieste Heart Muscle Disease Registry. Implantable cardioverter-defibrillator (ICD) has been implanted in 22 (11%) patients during follow-up. The end-points of the study were death/heart transplant and SD/appropriate ICD shock. 106 (50%) were asymptomatic at diagnosis. Considering symptomatic patients at diagnosis, heart failure (HF), chest pain, syncope and palpitations were the main symptoms in 29, 33, 15 and 23% of the cases respectively. During a mean follow-up of 118±87 months, 44 (21%) patients died/underwent heart transplant (D/HTx) (15 pump failure deaths, 14 SD, 5 non-cardiovascular deaths and 10 HTx). Six patients had at least one appropriate ICD shock. D/HTx was observed in 11 (10%) asymptomatic patients and in 33 (31%) symptomatic patients at diagnosis (p<0.016). At multivariate analysis a diagnosis in asymptomatic stage (HR 0.33, CI 95% 0.15-0.74, p=0.007), chest pain diagnosis (HR 0.21, CI 95% 0.05-0.89, p=0.034) and lower left atrium area (for every 1 cm2 decrease HR 0.95, CI 95% 0.92-0.98, p=0.02) emerged as independent predictors of survival-free from D/HTx. Conversely, a lower left ventricular ejection fraction (for every 10% decrease in LVEF) (HR 1.15, CI 95% 1.08-1.22, p<0.001) and restrictive pattern (HR 2.92, CI 95% 1.04-8.23, p=0.043) emerged as independent predictors of SD/appropriate ICD shocks.

**Conclusions:** Clinical presentation has a relevant prognostic role in HCM, since diagnosis in an asymptomatic stage and chest pain as main onset symptom were associated with a more favourable long-term outcome. Moreover, left atrium enlargement emerged as an independent predictor of D/HTx, whereas left ventricular ejection fraction and restrictive filling pattern were found to be independent predictors of SD or appropriate ICD shocks.
**Cardiomyopathies: prognosis**

### P4264

**Left ventricular reverse remodeling in idiopathic dilated cardiomyopathy: a subgroup analysis of the population enrolled at the Florence referral center for cardiomyopathies**

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**Purpose:** Idiopathic dilated cardiomyopathy (IDCM) is a myocardial disorder characterized by left ventricular dilation and systolic dysfunction. Recent data show that there is a positive correlation between the effect of optimal medical therapy on left ventricular reverse remodeling (LVR) and on mortality in heart failure (HF) and/or IDCM pts. Aims of our study were to determine survival rates in IDCM patients experiencing LVR and the potential role of cardiac resynchronization therapy (CRT).

**Methods:** Among 603 consecutive IDCM pts we studied a subgroup of 425 pts. 309 M (72.7%), mean age 53.5±12.12 yrs, with complete repeated echocardiographic evaluations. Mean indexed left ventricular (LV) end-diastolic diameter (EDD) was 35.1±5.0 mm/m². LV ejection fraction (EF) was 32.3±3.9%. NYHA class was 2.3±0.8. Pts were divided in three groups, based on enrollment periods: 1) 1977-1990 (n=71); 2) 1991-2000 (n=144); 3) 2001-2011 (n=210). The mean follow-up was 16.8±7.8, 10.9±5.0 and 6.3±3.9 yrs, respectively. No statistical difference was observed in gender, LV mass index, LV ejection fraction of LVEF, NYHA class at enrollment and atrial fibrillation at enrollment among the three groups. As expected medical therapy differed significantly with regard to use of ACE inhibitors/angiotensin receptor blockers, beta-blockers, anti-aldosterone drugs and digitals. For the purposes of the study we defined LVR as: 1) an increase in LVEF of at least 10 points or a decrease in EDD of at least 10% or LV EDD ≤33 mm/m². LVRR is related to a favorable prognosis, this finding being presumably related to the increasing use of evidence-based treatment of HF (mainly neurohormonal therapy).

**Results:** During follow-up 72 pts (18.9%) died due to refractory HF, 38 (8.9%) due to sudden death (SD), 17 (4.0%) of non cardiac causes, 21 pts (4.9%) underwent heart transplantation therapy (CRT).

**Conclusion:** Among IDCM pts experiencing LVRR and the potential role of cardiac resynchronization therapy on left ventricular reverse remodeling (LVRR) and on mortality in heart Failure is a challenging goal, given the limited amount of heart transplant donors for critically ill pts. We enrolled 603 consecutive IDCM pts (diagnosis made according to WHO criteria, all pts underwent coronary angiography to exclude a ≥50% stenosis of main branches), 442 M (73.3%), mean age 53.2±12.15 ys (range 16-75). Mean indexed left ventricular (LV) end-diastolic diameter (EDD) was 36.1±5.6 mm/m², LV ejection fraction (EF) was 31.9±5.7%, indexed left atrium diameter (LAD) was 23.9±4.5 mm/m² and mean NYHA class was 2.3±0.8. Pts were divided in four groups based on enrollment period: 1) 1977-1984 (n=66); 2) 1985-1990 (n=102); 3) 1991-2000 (n=197); 4) 2001-2011 (n=238). The mean follow-up was 9.4±6.0, 11.3±6.2, 10.1±5.3 and 6.6±3.9 yrs, respectively. No statistical difference was observed in gender, NYHA class and presence of atrial fibrillation at enrollment among the four groups. The use of ACE inhibitors/angiotensin receptor blockers and beta blockers therapy increased significantly during time.

**Purpose:** Determining the prognosis in idiopathic dilated cardiomyopathy (IDCM) is a challenging goal, given the limited amount of heart transplant donors for critically ill pts. In our study we aimed to find relevant prognostic factors in IDCM pts enrolled at our Center.

**Methods:** We enrolled 603 consecutive IDCM pts (diagnosis made according to WHO criteria, all pts underwent coronary angiography to exclude a ≥50% stenosis of main branches), 442 M (73.3%), mean age 53.2±12.15 ys (range 16-75). Mean indexed left ventricular (LV) end-diastolic diameter (EDD) was 36.1±5.6 mm/m², LV ejection fraction (EF) was 31.9±5.7%, indexed left atrium diameter (LAD) was 23.9±4.5 mm/m² and mean NYHA class was 2.3±0.8. Pts were divided in four groups, based on enrollment period: 1) 1977-1984 (n=66); 2) 1985-1990 (n=102); 3) 1991-2000 (n=197); 4) 2001-2011 (n=238). The mean follow-up was 9.4±6.0, 11.3±6.2, 10.1±5.3 and 6.6±3.9 yrs, respectively. No statistical difference was observed in gender, NYHA class and presence of atrial fibrillation at enrollment among the four groups. The use of ACE inhibitors/angiotensin receptor blockers and beta blockers therapy increased significantly during time. Survival rates for the entire population at 5, 10 and 15 years was 71%, 67% and 62%, respectively. Female gender (HR 0.56, 95% CI 0.41-0.77, p=0.005), age (HR 1.02, 95% CI 1.01-1.03, p=0.001) and NYHA class (HR 1.75, 95% CI 1.47-2.07, p<0.001), LV EF (HR 0.98, 95% CI 0.97-
0.99, p < 0.05) and iLA/D (HR 1.06, 95% CI 1.03-1.09, p < 0.0001) at enrollment were all significant prognostic factors.

Conclusions: Our data show the enrollment period as the most important prognostic factor in DCM pts enrolled at our Center, with a 75% relative risk reduction in overall mortality over the last thirty years, this finding being presumably related to the increasing use of evidence-based treatment of HF over time. Moreover female gender, age, NYHA class, UFEV and iLA/D at enrollment each portends a significant prognostic value.

P4268
Fragmented QRS complexes on 12-lead ECG predict myocardial fibrosis in hypertrophic cardiomyopathy

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Purpose: It is well-established that fragmented QRS complexes (fQRS) on the 12-lead electrocardiogram (ECG) are a predictor of delayed gadolinium enhancement (DGE) on Cardiac MRI (CMR) and indicate myocardial scarring in patients with coronary artery disease and dilated cardiomyopathy. Moreover, fQRS appear to correlate well with arrhythmic events and mortality in these cohorts. However the significance of fQRS in hypertrophic cardiomyopathy (HCM) is yet to be established. We sought to determine whether the presence og fQRS by 2 independent readers blinded to the CMR findings. Patients with documented myocardial infarction (n=3) were excluded from further analysis. The ECGs were correlated to CMR findings, and patients separated into DGE positive (DGE+; n=44) and negative (DGE-; n=35) groups. ECG territories of fQRS were correlated with myocardial segments of DGE on CMR, in order to determine whether areas of IQRs predicted areas of DGE.

Results: Patients from the DGE+ and DGE- groups were of similar gender (75% vs. 77% male respectively, p=0.10) and age (54±19 vs. 57±11 years respectively, p=0.41). Fragmented QRS complexes were significantly more prevalent in the DGE+ group than in the DGE- group (66.2% vs. 14.3%, p<0.001). The positive predictive value (PPV) of fQRS for DGE on CMR was 85.7%, with a specificity of 86.7%, sensitivity of 68.2% and negative predictive value of 68.2. In the DGE+ group with iQRs (n=30), iQRS ECG lead territory was predictive of regions of DGE on CMR in 73.3% (n=22) of patients.

Conclusions: The presence of iQRS on 12-lead ECG correlates with DGE on CMR in patients with HCM with good specificity and PPV. Electrocardiographic territories containing fragmentation also correlate with myocardial segments of DGE on CMR. This simple, inexpensive method may therefore be valuable for predicting scar or fibrosis in patients with HCM. Future work should focus on correlating iQRS with risk factors and events to determine its use in risk stratification.

P4269
Tissue Doppler imaging and prognosis in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy

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Aims: Assessment of left ventricular (LV) systolic and diastolic functions by tissue Doppler imaging (TDI) has been reported to be useful for predicting the prognosis in patients with hypertrophic cardiomyopathy (HCM). The purpose of this study was to evaluate the clinical significance of TDI parameters for prediction of cardiovascular events in asymptomatic or mildly symptomatic patients with HCM.

Methods and results: Eighty-five HCM patients (52 males, 55.6±14.8 yrs.) belonging to New York Heart Association (NYHA) functional class I or II were enrolled in this study. Patients with LV systolic dysfunction or a clinically documented history of atrial fibrillation were excluded. The combined end-points were HCM-related death, heart failure hospitalization, or resuscitated cardiac arrest. Moreover, high adverse outcome rate connected to MVO necessitates early recognition and appropriate therapeutic interventions.

Figure 1

Conclusions: HCM phenotype is associated with SD and associated arrhythmic events (ventricular tachycardia/fibrillation, resuscitated cardiac arrest and appropriate defibrillator discharge) rates among four discrete hypertrophic cardiomyopathy (HCM) phenotypes (asymmetric septal hypertrophy (ASH), mid left ventricular outflow tract obstruction (LVOTO) at rest, midventricular hypertrophy/obstruction (MVO) and apical hypertrophy (APH)) and to challenge the importance of hypertrophy type in SD prediction.

P4270
Importance of hypertrophy pattern in sudden death risk stratification among patients suffering from hypertrophic cardiomyopathy

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Purpose: To investigate differences in sudden death (SD) and associated arrhythmic events (ventricular tachycardia/fibrillation, resuscitated cardiac arrest and appropriate defibrillator discharge) rates among four discrete hypertrophic cardiomyopathy (HCM) phenotypes (asymmetric septal hypertrophy (ASH), LVOTO, mid left ventricular outflow tract obstruction (LVOTO) at rest, midventricular hypertrophy/obstruction (MVO) and apical hypertrophy (APH)) and to challenge the importance of hypertrophy type in SD prediction.

Methods: Hypertrophy phenotypes were recognized by means of echocardiography and MRI in 423 HCM patients (49.3±17.2 years, 66.2% male) followed up for a median of 84 months (7 years, range 6 to 480 months). Cumulative SD event rates through follow up were estimated by Kaplan-Meier method and differences were assessed by log rank test. To identify independent predictors of the study outcome, univariate and multiple Cox proportional hazard models were adopted. p-values < 0.05 were considered significant.

Results: ASH was discovered in 259 patients (61.2%), LVOTO in 88 (20.8%), MVO in 34 (8%), and APH in 42 (9.9%). MVO was independently associated with SD and with significant hazard ratio (HRR): 3.3, 95% CI 1.26-8.85, p=0.016) independently of the 5 established risk markers for SD (family history of SD, syncope, non sustained ventricular tachycardia, abnormal blood pressure response during exercise and maximum wall thickness > 3.0 cm).

Conclusion: Patients with documented myocardial fibrosis in hypertrophic cardiomyopathy

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P4271
Prognostic role of a high-sensitivity cardiac troponin T marker in patients with dilated cardiomyopathy

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Purpose: Although serum high-sensitivity cardiac troponin T (hs-cTnT) has become a well established diagnostic and prognostic marker in acute coronary syndrome, the prognostic significance of a hs-cTnT marker in dilated cardiomyopathy (DCM) is unclear. The aim of this study was determine whether hs-cTnT can be a reliable prognostic marker of cardiac events in DCM.

Methods: We performed clinical evaluation including measurement of hs-cTnT in 55 patients with DCM. The normal range of hs-cTnT is less than or equal to 0.014 ng/mL. hs-cTnT concentrations (0.015-0.028 ng/ml) and very high concentrations (0.028 ng/ml >) were considered significant.

Results: hs-cTnT concentrations (0.015-0.028 ng/ml) and very high concentrations (0.028 ng/ml >) were considered significant.

Conclusion: hs-cTnT can be a reliable prognostic marker of cardiac events in DCM.

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Number of morphological kinds of ventricular premature beats with fragmented QRS waves on 12-lead holter ECG predicted left ventricular fibrosis and fatty change on CT in hypertrophic cardiomyopathy

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**Purpose:** To determine the number of morphological kinds of ventricular premature beats (VPB) with fragmented QRS waves (FQRSW) on 12-lead Holter ECG in presence of the left ventricular (LV) fibrosis or fat on CT in hypertrophic cardiomyopathy (HCM) subjects.

**Methods:** This was a retrospective analysis of 49 consecutive HCM subjects who underwent CT (Aquilion one) and 12-lead Holter ECG (RAC-2103) within 3 months. If there was a contrast defect in myocardium in early phase, late phase acquisition was added, and if abnormal late enhancement was observed in the corresponding site, we diagnosed myocardial fibrosis. If contrast defect continued in late phase with CT values < 0 HU, we diagnosed myocardial fatty change. Sensitivity and specificity for detection of fibrosis and fat were 71.4 and 66.7% (fibrosis), and 58.3 and 45.9% (fat) in subjects with fibrosis than in those without (both P<0.01), but there was no significant differences in the numbers of morphological kinds of both all VPB and VPB with FQRSW between the subjects with fat and those without. According to a receiver operating characteristic curve, best cutoff value for number of morphological kinds of VPB with FQRSW as 2 for fibrosis and 3 for fat. Sensitivity and specificity for detection of fibrosis and fat were 71.4 and 66.7% (fibrosis), and 50.0 and 73.0% (fat) in number of morphological kinds of VPB with FQRSW, respectively and those were 82.1 and 53.1% (fibrosis), and 58.3 and 45.9% (fat) in number of morphological kinds of all VPB, respectively.

**Results:** Fibrosis and fat were observed on CT in 28 and 15 subjects, respectively. The numbers of morphological kinds of both all VPB and VPB were greater in subjects with fibrosis than in those without (both P<0.01), but there was no significant differences in the numbers of morphological kinds of both all VPB and VPB with FQRSW on 12-lead Holter ECG.

**Conclusions:** Serum concentrations of hs-cTnT level was a useful prognostic predictor in DCM patients.

Severe myocardial fibrosis detected by cardiac MRI in patients with hypertrophic cardiomyopathy is associated with high risk for future arrhythmic events

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**Study aim:** To correlate the incidence of adequate ICD interventions in hypertrophic cardiomyopathy (HCM) with the presence of the different classical risk markers (RM) for sudden cardiac death (SCD) plus myocardial fibrosis as detected by gadolinium-enhanced MRI (GE-MRI).

**Methods:** We analyzed 86 patients with HCM that had ICD implantation, either for secondary (n=23), or primary prophylaxis of SCD (n=73). For fibrosis assessment, patients underwent prior GE-MRI. Fibrosis was scored using a 17-segment LV model (from 0-absent, 1-point-shaped, 2-limited to 1 LV segment, 3-involving ≥2 segments). ICD memories were regularly read out and interpreted in accordance with established guidelines. Sensitivity and specificity for detection of fibrosis and fat were 71.4 and 66.7% (fibrosis), and 50.0 and 73.0% (fat) in number of morphological kinds of VPB with FQRSW, respectively and those were 82.1 and 53.1% (fibrosis), and 58.3 and 45.9% (fat) in number of morphological kinds of all VPB, respectively.

**Results:** The number of RM per patient was 1.7±1.0. Myocardial fibrosis on GE-MRI was present in 71 pts (96%), of which 38 pts (51%) had a fibrosis score of 3. During follow up of 2.4±2.4 (0.1-9.2) years, 46 adequate ICD interventions (10 discharges, 36 episodes of antitachycardia pacing) were documented in 12 pts. ICD membranes were regularly read out and interpreted in accordance with established guidelines. Sensitivity and specificity for detection of fibrosis and fat were 71.4 and 66.7% (fibrosis), and 50.0 and 73.0% (fat) in number of morphological kinds of VPB with FQRSW, respectively and those were 82.1 and 53.1% (fibrosis), and 58.3 and 45.9% (fat) in number of morphological kinds of all VPB, respectively.

**Conclusions:** In this carefully selected cohort of HCM pts. considered to be at high risk, the event rate was indeed high. Severity of myocardial fibrosis as detected by GE-MRI seems to be associated with future arrhythmic events.

Are different ballooning patterns in stress-induced (Takotsubo) cardiomyopathy associated with different clinical backgrounds and outcomes?

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**Purpose:** Takotsubo cardiomyopathy (TCM) was initially defined as a stress-related acute coronary syndrome-like clinical disorder typically with "transient left ventricular apical ballooning" without coronary stenosis (type A). However, reports of a variant form of TCM with non-apical ballooning (type non-A) have been accumulating. We examined whether type non-A/TCM has the same clinical characteristics and long-term prognosis as those of type A.

**Methods:** Data on TCM (n = 199) were retrieved from the BOREAS (Broad-range cooperative Organization for Renal, Arterial and cardiac Studies) registry and analyzed for differences in clinical features and outcome between type A (n=171, 86%) and type non-A (n=28, 14%) TCMs.

**Results:** (1) There were no significant differences in age, proportion of females, and number of coronary risk factors between type A and type non-A TCMs. However, underlying disease was different between the two types: intracranial bleeding was more frequent [type A=13% vs. type non-A=4%] and phenochromocytoma was much less frequent [type A=1% vs. type non-A=18%] in type A than type non-A.

**Conclusions:** Serum concentrations of hs-cTnT level was a useful prognostic predictor in DCM patients.
Prognostic value of the admission ECG for predicting complications in patients with tako-tsubo cardiomyopathy

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Purpose: Tako-tsubo cardiomyopathy (TTC) mimics acute myocardial infarction. A substantial number of patients develop adverse events during the acute course of TTC.

Methods: We prospectively monitored 76 TTC patients (69±7 years; 70±12 years). A total of 37 patients (49%) developed one (n=17) or more (n=20) adverse events such as pulmonary edema (n=14), cardiogenic shock (n=4), ventricular tachycardia (n=7), atrial fibrillation (n=14), right ventricular involvement (n=5), intraventricular pressure gradient (n=6), thrombus and/or stroke (n=6), or death (n=2). Clinical parameters and the admission ECG were compared in patients with and without adverse events.

Results: Patients with adverse events were older (73±12 vs 67±12 years, p=0.05) and more frequently female (52% vs 14%, p=0.05). There was a higher rise in troponin (9.4±9.0 vs 6.1±5.7 times the upper limit of normal, p=0.05) and a lower left ventricular ejection fraction (47±13 vs 55±13%, p=0.007) in patients with adverse events. Angiographic ballooning pattern and left ventricular end-diastolic pressure were not different.

Conclusion: Almost half of the patients with TTC develop adverse events. Especially elderly females with a high heart rate and a prolonged QTc interval on the admission ECG were closely monitored in type A TTC, especially in cases with intraventricular obstruction.

Identification of patients with idiopathic dilated cardiomyopathy and SCD-HeFT inclusion criteria who could be considered for early ICD implantation

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Purpose: To identify patients with recently diagnosed idiopathic dilated cardiomyopathy (IDC) and symptomatic heart failure unlikely to improve despite medical treatment introduction/optimization and who could be considered for early ICD implantation.

Methods and Results: 189 consecutive patients with IDC and SCD-HeFT criteria (LV ejection fraction <0.35 and NYHA classes II-III) evaluated before starting betablocking treatment were enrolled in the Trieste Heart Muscle Disease Registry. After optimization of medical treatment only 58 patients (31%) maintained SCD-HeFT criteria 6 months later. A multivariable analysis revealed in the Cox model (n=12, 6%, 4 died suddenly). According to the multivariable analysis, the presence of an adverse event at the first diagnostic LV volume >110 ml/m² (OR=2.63; 95% CI 1.29-5.60), lower systolic blood pressure (OR for interquartile difference=1.36; 95% CI 1.33-1.40), a larger indexed left atrial diameter (OR for interquartile difference=1.72; 95% CI 1.07-2.78), the presence of left bundle branch block (OR=2.17; 95% CI 1.06-4.43) and the presence of significant coronary revascularization (OR=2.18, 1.05-4.5) significantly predicted the persistence of IDC inducible death 6 months later. Considering these parameters a model for the probability of non improvement estimation was developed.

Conclusions: In IDC, only a minority of patients still have SCD-HeFT criteria after optimization of medical treatment or die in the meanwhile; applying simple clinical parameters it is possible to identify this patients, who could be considered for earlier ICD implantation.

Long-term follow-up of 99 patients after transcoronary ablation of septal hypertrophy (TASH) for HOCM: No evidence for the induction of an arrhythmogenic substrate

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Background and Aim of the study: Prognosis after surgical myectomy for HOCM is beneficial even in long-term follow-up. However, after TASH only mid-term follow-up data is available so far. In the present study we systematically analyzed the mortality in a 7 year follow-up after TASH.

Methods: All patients who underwent TASH-treatment at our institution within the year 2004 were included in the study (n=103, age 57.6±15 years). Follow-up was performed by telephone contact with either the patients or their general practitioners. Only patients who lived abroad (Syria, Australia, Turkey, Italy) were lost in follow-up and were excluded from the study.

Results: Left ventricular outflow tract (LVOT) obstruction decreased significantly after the injection of 0.94±0.3 ml of ethanol (LVOT gradient at rest pre vs. post TASH: 76.0±17.5 mmHg, after provocation pre vs. post TASH: 163.6±60.4 mmHg; p<0.0001 for all). No patient died during the TASH-procedure or during the hospital stay. In 10 patients TASH was a redo intervention. During a mean follow-up time of 6.5±1.4 years 10 patients died. 7 patients died from non cardiac reasons (5.6±0.8 years after TASH) and 3 patients died suddenly (2, 9 and 79 months after TASH at the age of 57, 47 and 79 years). In this study population the yearly total mortality was 1.6%, the yearly sudden death rate 0.4% and the in hospital mortality 0%.

Conclusion: Prognosis after TASH is excellent even in long-term follow-up. The sudden death rate in this study population is lower compared to untreated HOCM patients. There is no evidence for the induction of an arrhythmogenic substrate after alcohol ablation.

Surgical correction of HOCM in patients with severe hypertrophy and septal myocardial fibrosis

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Purpose: The mechanism of sudden death in HOCM is ventricular tachycardia/arrhythmia emanating from areas of fibrosis. The classic Morrow technique for HOCM in patients with extreme left ventricular hypertrophy, right ventricular obstruction and myocardial fibrosis is not effective. A new technique of HOCM surgical correction in patients with severe hypertrophy and septal myocardial fibrosis was proposed.

Methods: The excision of the asymmetrical hypertrophied area of the interventricular septum (IVS) causing LVOT and RVOT obstruction simultaneously was performed from the canal part of the interventricular septum, so that the zone of ventricular obstruction and myocardial fibrosis was not effective. A new technique of HOCM surgical correction in patients with severe hypertrophy and septal myocardial fibrosis was proposed.

Results: In IDC, only a minority of patients still have SCD-HeFT criteria after optimization of medical treatment or die in the meanwhile; applying simple clinical parameters it is possible to identify this patients, who could be considered for earlier ICD implantation.

Conclusions: In IDC, only a minority of patients still have SCD-HeFT criteria after optimization of medical treatment or die in the meanwhile; applying simple clinical parameters it is possible to identify this patients, who could be considered for earlier ICD implantation.
**P4280 Long-term recovery of ativoventricular conduction after percutaneous translesional septal myocardial ablation in patients with hypertrophic obstructive cardiomyopathy**

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**Objectives:** Lesion of the ativoventricular (AV) conduction system is a well known adverse effect of percutaneous translesional septal myocardial ablation (PTMSA) in patients with hypertrophic obstructive cardiomyopathy (HOCM). Implantation of permanent pacemakers (PM) following PTMSA has been reported in 3 to 38% of patients, but data determining potential long-term AV recovery is sparse.

**Methods:** The AV-conduction was evaluated by ECG and 48 hours Holter recording at long-term follow-up 4.8±3.6 years after PTMSA. In patients with a PM or implantable cardioverter defibrillator (ICD) the device was adjusted to back-up VVI-mode frequency 40. Documented high grade AV block defined as 2nd or 3rd degree was registered.

**Results:** Eighty six of 101 consecutive patients undergoing first time PTMSA from 1999-2011 (age 61±12 years) had no implantable device at baseline. Left bundle branch block was present in 7% and right bundle branch block in 23% of the patients at baseline. Twenty eight percent (24/86) of the patients without a device at baseline had a PM implanted for high grade AV block 6.4±2.8 days after PTMSA (n=13), and 6.4±1.8 days after PM implantation (n=4). The follow-up period ranged from 6 to 7 years after PTMSA in 6.5 to high grade AV block. Patients who had a PM implanted in relation to PTMSA were significantly older (66±10 vs. 59±13 years, p=0.02) and they had higher incidence of AV block during the procedure (67 vs. 33%, p<0.01) than those who did not.

Eight patients with PTSMA-related PMs were diseased at the time of follow-up and two patients declined participation in the long-term evaluation of AV conduction. In 43% (6/14) of patients 48 hour Holter recordings did not reveal high grade AV block which suggests post-discharge recovery of the AV conduction. No significant differences in baseline characteristics were found between patients with documented high grade AV block and those without.

**Conclusions:** After first time PTMSA a PM was implanted due to AV block in 26% of patients with no previously implanted device. The long-term evaluation of AV conduction showed spontaneous recovery in 43% of these patients. This post-discharge recovery of the AV-conduction after PTMSA might suggest the potential for a more conservative pacemaker strategy.

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**P4281 Long-term outcomes after heart transplantation for Emery-Dreifuss muscular dystrophy**

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**Background:** Emery-Dreifuss muscular dystrophy (EDMD) is an hereditary syndrome related to mutations in lamin A/C gene (LMNA) and is characterised by severe dilated cardiomyopathy, mostly slight peripheral muscular dysrophy, supraventricular arrhythmia and ativoventricular (AV) block. Transplantation for EDMD is rarely reported in the ISHLT registry. We aim to study outcomes after heart transplantation (HTx) for end-stage heart failure in twelve EDMD patients.

**Methods:** 12 cases of HTx performed for EDMD confirmed by genetic analysis in a single institution between 1997 and 2011 were compared to 12 patients age, sex and year of transplantation matched. Survival curves were analyzed by Kaplan-Meier method.

**Results:** Before transplantation, EDMD patients had similar age (56 vs 57 yo, p=0.81), sex ratio (42% male), pre-transplantation NYHA functional class III (p=0.207), left ventricular ejection fraction (LVEF) (63% vs 32%, p=0.89), higher rate of supra-ventricular arrhythmia (100% vs 45%, p<0.002) and AV block (58% vs 12.5%, p=0.042) compared to non-EDMD. After HTx, NYHA functional class was similar (I, p=1.00), LVEF (72±5.9% vs 69±11.3%, p=0.49), rejection rate (19%±3.8% vs 40%±8.2% by year, p=0.45), infection rate (14% vs 6% by year, p<0.007), renal function (eGFR=89±49 vs 66±37 ml/min, p=0.22) were similar after HTx in EDMD and non-EDMD group. Survival rate at 1 year, 5 years and 7 years were not significantly different (respectively 91.6%, 90.9%, 81.5% versus 100%, 100%, 100%, p=0.146). 42% EDMD patients had slight muscular dysfuncion, comparable with good quality of life.

**Conclusion:** Despite reluctance for heart transplantation in end-stage HF patients with EDMD, long term outcomes are similar to non EDMD patients at 1.2 and 5-year follow-up in our institution.

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**P4282 Distinguishing 320-slice CT-detected focal fibrotic lesions and non-fibrotic lesions in hypertrophic cardiomyopathy by assessment of regional myocardial-strain using two-dimensional Speckle-tracking**

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**Purpose:** To distinguish focal fibrotic and non-fibrotic-lesions in LVM in HCM subjects, we compared myocardial-regional-peak-strain-values using two-dimensional speckle-tracking transthoracic-echocardiography (TTE) in 320-slice-CT-detected fibrotic, non-fibrotic and normal-control-lesions.

**Methods:** Forty-subjects (20-consecutive-HCM-subjects (mean 59.1 years), 20-healthy-controls (mean 61.4years)) underwent speckle-tracking TTE, and analysis of regional-peak-longitudinal (LS) and transverse-strain (TS) in each of 17-LVM-segments (American-Heart-Association classification). In HCM-subjects, fibrotic-lesions were identified by early-phase defective-enhancement and late-phase abnormal-enhancement by 320-slice-CT. Regional-peak-LS and TS were measured in MSCI-detected fibrotic and non-fibrotic LVM lesions.

**Results:** In 20-HCM-subjects, 318-lesions (93.0%) yielded good-tracking on TTE. LV-lesions showed fibrotic-change in 10-subjects. Regional-peak-LS absolute-values were significantly lower in fibrotic-lesions than in non-fibrotic-lesions in HCM-subjects and controls (5.6±2.9%, 11.1±5.7%, 14.6±6.2%, respectively), furthermore these were significantly lower in non-fibrotic-lesions in HCM-subjects than controls (P<0.001). However there were no significant-differences of regional-peak-TS among fibrotic and non-fibrotic-lesions in HCM-subjects and controls (10.0±12.7%, 13.2±8.4%, 14.6±11.1%, respectively).

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**P4283 Hidden right ventricular dysfunction in asymptomatic first-degree relatives of arrhythmogenic right ventricular cardiomyopathy assessed by speckle tracking, compared with strain Doppler**

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**Purpose:** According to modifications of criteria of ARVC, proposed to facilitate clinical diagnosis in first-degree relatives, who often have incomplete expression of the disease, the diagnosis of familial ARVC is based on one of the following findings: either mild global dilatation or reduction in RV ejection fraction (EF) with normal LV or mild segmental dilatation of the RV or regional RV hypokinesis. The potential utility of Strain-Strain rate (S-SR) Doppler and two-dimensional (2D) to quantitatively assess RV (TAPVR and RA/right atrium) function in asymptomatic family members of ARVC, with apparently normal RV, was evaluated.

**Methods:** 80 subjects were studied: 40 first degree ARVC relatives with normal RV at standard echocardiography and 40 healthy controls. By E9-GE LV EF, LV diameters and volumes, RV dimension, fractional area change (FAC%) and RVO fractional shortening (RVT0%), RA volume were measured. By DTI velocity of early (E) and late (A) diastolic and systolic wave (S) at tricuspid annulus was measured. Longitudinal systolic RV S-SR Doppler and 2D S-SR in apical 4 and 2-chambers views were measured at level of RV free wall segments, all LV segments and RA wall. Circumferential and radial systolic LV 2D S-SR were measured in middle short axis view. By 3D echocardiography with volumetric probe we measured RA and RV volumes.

**Results:** No significant differences were found between relatives and controls for RV dimensions (15±2.0 to 16±1.9 cm). RVFAC (50±12 vs 51±11%) and RVT0% (64±8.1% vs 63±5.3%); RA max volumes by 2D (39±8.5 vs 37±7.5 ml; index: 20±3.4 vs 8.7±1.6 ml/m²) and by 3D (52±9.6 vs ±51±13 ml; index: 27±4.5 vs 28±10 ml/m²). 3D RV end-diastolic (31±10.5 vs 33±11 ml/m²)
Cardiac sarcoidosis has characteristic distribution of late gadolinium enhancement in magnetic resonance imaging in comparison with idiopathic dilated cardiomyopathy

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Purpose: Late gadolinium enhancement (LGE) in cardiac magnetic resonance (CMR) imaging is useful for the early diagnosis of cardiac sarcoidosis (CS). However, since some patients with dilated cardiomyopathy (DCM) also exhibit LGE, the differential diagnosis is sometimes difficult. This study aimed to identify the characteristic distribution of myocardial LGE in CS and to compare LGE patterns in CS with DCM.

Methods: Eighty one patients with suspect of CS and 52 patients with DCM underwent CMR imaging. The intra-leaflet ventricular (LV) and intra-mural distribution of LGE was compared.

Results: LGE was present at 22 patients (27%) with suspect of CS and 30 patients (58%) with DCM. In patients with CS, LGE was distributed into all LV segments, whereas LGE localized mainly in basal inter-ventricular septum in patients with DCM. The intra-mural analysis demonstrated that LGE was distributed into subepicardial to subendocardial layers in patients with CS, whereas LGE localized mainly in the mid-ventricular layer in patients with DCM. Especially, subepicardial and subendocardial LGE (with spared mid-ventricular layer), circumferential subepicardial LGE, and nodular (transmural) LGE were characteristic patterns in CS. The sensitivity and specificity were 23% and 97% in subepicardial and endocardial LGE, respectively.

Conclusions: Characteristic patterns of LGE in CS can help differential diagnosis of CS from DCM.

Figure 1. Characteristic patterns of LGE in CS

Conclusions: In patients with CS, LGE-CMR showed more diffuse distribution of LGE compared with patients with DCM. The characteristic patterns of LGE distribution can help differential diagnosis of CS from DCM.

Traditional and innovative echocardiographic parameters for the analysis of right ventricular performance in comparison to cardiac magnetic resonance

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Background: Right ventricular fractional area change (RVFAC), tissue Doppler and M-mode measurements of tricuspid systolic motion (tricuspid Sm and TAPSE) are the only current non invasive methods for the quantification of RV systolic function; RV deformation analysis by speckle tracking echocardiography (STE) has recently allowed the analysis of RV performance. Using cardiac magnetic resonance (CMR) as the reference standard, this study aimed at exploring the correlation between these traditional and innovative echocardiographic parameters and RV ejection fraction (RVEF) measured by CMR.

Methods: CMR and transthoracic echo-Doppler were performed in 54 patients referred for clinical assessment (ejection fraction 41±6.15±6%). 32 presented the suspicion of myocarditis, 18 of hypertrophic cardiomyopathy, 4 of arrhythmogenic right ventricular dysplasia. RVEF was measured by MRI. RVFAC, tricuspid Sm and TAPSE were calculated in all patients. RV longitudinal strain (S-SR) by STE was assessed averaging RV free wall segments (five wall RVLS) and by averaging all segments (global RVLS). The ROC analysis was applied for the assessment of diagnostic accuracy.

Results: Significant correlations were found for TAPSE, tricuspid Sm and global RVLS with RVEF (r=0.46, r=0.94 and r=-0.63, p<0.01 for all, respectively). Close correlations of free wall RVLS and RVFAC with RVEF were found (r=0.86 and r=-0.82, respectively; p<0.001 for both). Furthermore, free wall RVLS demonstrated the highest diagnostic accuracy (AUC of 0.91) and good sensitivity and specificity of 96% and 92%, respectively, to predict reduced RVEF above 45%, using a cutoff value less than -17.0%.

Conclusions: In a group of patients referred for cardiac CMR evaluation, TAPSE, tricuspid Sm and global RVLS correlated with RVEF obtained by CMR. Free wall RVLS and RVFAC correlated well with RVEF, providing a better estimation of RV systolic performance.
Conclusions: Myocardial fibrosis in HCM is a progressive phenomenon, related to a worse clinical status. Apical hypertrophic cardiomyopathy is probably characterized by a larger increment of LGE than other patterns.

Methods: 55 HCM patients (37 males; mean age 43.±18 years) underwent two CMR examinations (CMR-1 and CMR-2) separated by an interval of 719±410 days. Extent of LGE was measured and the rate of progression of LGE (LGE-rate) was calculated as the ratio between the increase of LGE in (grams) and the time (months) between the CMR examinations.

Results: At CMR-1 LGE was detected in 45 subjects, with an extent of 13.3±15.2 grams. At CMR-2, 53 (96.4%) patients had LGE, with an extent of 24.6±27.5 grams. Patients with apical HCM had higher increment of LGE (p=0.004) and LGE-rate (p=0.001) than those with other patterns of hypertrophy (figure). The extent of LGE at CMR-1 and the apical pattern of hypertrophy were independent predictors of the increment of LGE. Subjects with worsened NYHA class presented higher increase of LGE (p=0.031) and LGE-rate (p=0.05) than those with preserved functional status.

Conclusions: DM increases the risk for cardiac complications, HF, hyperkinetic arrhythmias and myocardial fibrosis.

P4289

Left ventricular hypertrophia in individuals with sickle cell anaemia: pathophysiology or pathology?

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Introduction: Left ventricular noncompaction (LVNC) cardiomyopathy is rare amongst Caucasians but studies in African/Afro-Caribbean origin (black) heart failure patients demonstrate that a high proportion fulfill criteria for LVNC (30%). Recent observations in elite athletes, have also demonstrated a 3-fold greater prevalence of increased LV trabeculations (LVHT) amongst black athletes compared with Caucasian athletes, with almost 15% fulfilling echocardiographic criteria for LVNC. We postulate that the LVHT observed in black individuals represents an ethnically determined cardiac response to increased preload. Sickle cell anemia is associated with an increased preload and a high cardiac output. The aim of this study was to evaluate the prevalence of LVHT amongst homozygous sickle cell disease patients.

Methods: Between 2005 and 2012, 99 consecutive normotensive sickle cell patients (53% male) underwent echocardiography. Echocardiograms were analysed for trabeculations defined as localised protrusions of the ventricular wall >3mm in thickness associated with intertrabecular recesses and previously published criteria for LVNC. The results were compared with 132 healthy black controls (55% male).

Results: Sickle cell patients were older compared with controls (33.±11 years vs 21.±6 years; p<0.0001) with no difference in systolic BP (118±11mmHg vs 120±15mmHg; p=0.165) in either group. Sickle cell patients had a mean Hb level of 8.6±1.2g/dl (range 5.5g/dl-11.6g/dl). Sickle cell patients displayed a higher prevalence of LVHT compared with controls (28.3% vs 12.1%; p=0.0002). Of the sickle cell patients, 20.8% fulfilled conventional Chin et al and 10% Jeinn et al criteria for LVNC. None of the controls fulfilled the published LVNC criteria.

Sickle cell patients with LVHT exhibited a larger LV cavity size compared to controls with LVHT (51.7±6.0mm; range 44-66mm vs 47.1±6.0mm; range 38-54mm; p<0.0001) but showed no difference in LVIDd compared with Sickle cell patients without LVHT (mean LVIDd was51.1mm ± 5.6mm vs 51.9mm ± 6.1mm; p=0.604). There were no differences in LV systolic or diastolic function in sickle cell patients with or without LVHT (EF’ by Simpson was 61±8.1% vs 61±8.4%; p=0.985; E/A ratio was 2.0±0.8 vs 1.7±0.6; p=0.111 and MV deceleration 191±36ms vs 194±51ms; p=0.792).

Conclusion: The high prevalence of LVHT in sickle cell patients compared with healthy controls further reinforces the likelihood of this morphological anomaly representing a physiological response to increased cardiac preload and endorses the need for robust criteria for diagnosing LVNC in black individuals.

P4290

T1 mapping in differentiation of diffusive myocardial disease in hypertrophic and dilative cardiomyopathy

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Background: T1 mapping was proposed as a potentially valuable in quantitative assessment of diffuse myocardial fibrosis. We aimed todetermine its role in differentiation of healthy myocardium from diffuse fibrosis clinical setting.

Methods and results: Thirty-nine subjects with known hypertrophic (HC) or dilative cardiomyopathy (DCM) were enrolled (age 47±7.4 years). Twenty-five age-gender matched subjects with low pre-test likelihood ofcardiomyopathy served as controls. Single equatorial short-axis slice T1mapping was performed on a 3 Tesla scanner prior and at 10, 20 and 30 minutes afteradministration of 0.2 mmol/kg of gadobutrol. We quantified T1 values within the septal myocardium for both HC and DCM groups. 

Figure 1

Table 1

<table>
<thead>
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<th>Adjusted for no-MIO and covariate</th>
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<td>OR (95% CI)</td>
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<td>Cardiac fibrosis</td>
<td>4.23 (2.65-6.76)</td>
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<td>Heart failure</td>
<td>3.14 (1.87-5.26)</td>
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<td>LV dysfunction (LV and/or RV)</td>
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<tr>
<td>RV dysfunction</td>
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Co-variables: age, gender, comorbidity, age and anencephaly comorbidity
Effect of physical exercise on cardiac remodeling and oxidative stress in diabetic rats

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Purpose: Oxidative stress is one of the main mechanisms involved in the pathogenesis of diabetic cardiomyopathy. Studies suggest that physical exercise (PE) improves myocardial glucose homeostasis and reduces myocardial damage from diabetes mellitus (DM). The aim of this study was to evaluate the effect of PE on myocardial oxidative stress and in vivo and in vitro cardiac structure and function in diabetic rats.

Methods: Male Wistar rats were divided into three groups: control sedentary (CS, n=15), diabetic sedentary (DS, n=15), and diabetic trained (DT, n=15). Diabetes mellitus was induced by intraperitoneal injection of streptozotocin (50mg/kg, single dose). Physical training was performed 5 times a week for 8 weeks in a treadmill. All at the end of the experimental period, rats underwent echocardiography. Myocardial function was evaluated in left ventricular (LV) papillary muscle preparations during isometric contractions. Oxidative stress was measured in LV myocardial specimens. ANOVA was used to compare echocardiographic and oxidative stress parameters, and ANCOVA for papillary muscle parameters using papillary muscle cross sectional area as the co-variant, both complemented by the Tukey test (* p<0.05 vs. DS; # p<0.05 vs. CS).

Results: Echocardiogram showed increased LV diastolic diameter in the diabetic groups. Left atrium diameter was enlarged in diabetic rats and unchanged in CS. LV posterior wall shortening velocity was depressed in DS and DT. Papillary muscle cross-sectional area was depressed in both diabetic groups. Myocardial relaxation was depressed in the sedentary diabetic group; PE attenuated this change. Oxidative stress was increased in the diabetic groups and attenuated by PE (lipid hydroperoxide: CS 148±9; DS 302±26; DT 211±44; mg/dl; catalase: CS 125±7; DS 80±7.1; DT 107±17; nmol/ml; glutathione peroxidase: CS 29.7±1.7; DS 17.4±3.3; DT 23.1±4.2; nmol/ml).

Conclusions: Diabetes mellitus-induced impairment of oxidative stress and in vitro and in vivo cardiac structure and function is attenuated by physical exercise.

Dual assessment of coronary flow reserve in non obstructive hypertrophic cardiomyopathy: patophysiologcal charachteristics


Microvascular dysfunction reflected by the decreased coronary flow reserve (CFR) is a common finding in hypertrophic cardiomyopathy (HCM) and is related with unfavorable long term outcome. Elevated LV filling pressure and wall stress (as a result of diastolic dysfunction) might additionally aggravate CFR. Plasma levels of NT-pro-BNP and the ratio of early to late transmural vascular flow to early diastolic lateral mitral annulus velocity (E/e’) have been shown to be accurate non-invasive predictors of the abnormal LV wall stress and elevated LV filling pressure. Therefore, the aims of the current study were to examine: 1. Possible regional difference of CFR in hypertrophied (left anterior descending coronary artery (LAD) region) and nonhypertrophied (right coronary artery (RCA)) region 2. Relation between microvascular function, plasma levels of NT-pro-BNP and the ratio of E/e’.

Methods: In 41 pts (mean age 46±16 yrs;19 male) with asymmetric nonobstructive HCM (CHM) and is related with unfavorable long term outcome. Elevated LV filling pressure and wall stress (as a result of diastolic dysfunction) might additionally aggravate CFR. Plasma levels of NT-pro-BNP and the ratio of early to late transmural vascular flow to early diastolic lateral mitral annulus velocity (E/e’) have been shown to be accurate non-invasive predictors of the abnormal LV wall stress and elevated LV filling pressure. Therefore, the aims of the current study were to examine: 1. Possible regional difference of CFR in hypertrophied (left anterior descending coronary artery (LAD) region) and nonhypertrophied (right coronary artery (RCA) region) 2. Relation between microvascular function, plasma levels of NT-pro-BNP and the ratio of E/e’.

Results: Even though there was significant asymmetrical septal hypertrophy (ratio of septal/posterior wall thickness 1.9±0.6), there was no significant difference between CFR LAD and CFR RCA in non obstructive HCM (2.22±0.50 vs. 2.27±0.50, p=ns). Levels of NT-pro-BNP were significantly inversely correlated with CFR LAD (r=-0.57, p<0.001) and CFR RCA (r=-0.68, p<0.001). Also there was significant negative correlation between (E/e’) and CFR LAD (r=-0.53, p<0.001) and CFR RCA(r=-0.51, p=0.002).

Conclusion: In patients with asymmetric nonobstructive HCM, coronary microvascular function is both impaired in hypertrophied and non hypertrophied region. Elevated left ventricular wall stress and LV filling pressures significantly aggravate existent microvascular dysfunction.

Cyclophilin A expression in endomyocardial biopsies predicts clinical outcome of patients with congestive heart failure

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Background: Recently, we have identified Cyclophilin A (CyPA) and its extra-cellular receptor EMMPRIN (CD147) as novel diagnostic markers of inflammatory cardiomyopathies. Here, we evaluated the prognostic relevance of CyPA and EMMPRIN expression in endomyocardial biopsies of consecutive patients with congestive heart failure.

Methods: We enrolled 227 unselected patients with congestive heart failure undergoing endomyocardial biopsy for diagnostic reasons. Biopsies were analyzed using established histopathological and immunohistochemical criteria together with CyPA and EMMPRIN staining. Study endpoint was the composite of all-cause mortality, heart transplantation, malignant arrhythmia, and heart failure-related rehospitalization.

Results: CyPA was significantly enhanced in patients with inflammatory cardiomyopathy (n=127) as compared to patients with non-inflammatory cardiomyopathy (n=100, p<0.0001). In contrast, expression of EMMPRIN was similar in both subgroups (p=0.081). During a mean follow-up of 16.3 months 60 patients (27%) reached the endpoint. Of all clinical (ejection fraction, NYHA functional class), laboratory (BNP) and immunohistochemical parameters tested (CyPA, EMMPRIN, CD 68, CD3, MHC II, virus genome), CyPA was identified as the only independent predictor for the primary endpoint yielding a relative risk of 2.5 (95% CI 1.2-5.5, p=0.016 figure) as well as a relative risk of 4.7 for all-cause mortality and heart transplantation alone (95% CI 1.1-19.8, p=0.038). Subgroup analysis also revealed CyPA as a predictor of outcome in the patients with non-inflammatory cardiomyopathy suggesting that CyPA is a prognostically relevant marker of myocardial damage beyond inflammation.

Impaired copper homeostasis in patients with hypertrophic cardiomyopathy

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Purpose: Hypertrophic Cardiomyopathy(HCM) is the commonest monogenetic inherited cardiac disorder, characterised by increased ventricular wall thickness, myocyte disarray and myocardial fibrosis. Recently, HCM has been associated with enhanced oxidative stress, which in turn has the potential to perpetuate hypertrophy and myocardial fibrosis. Myocardial copper and zinc imbalance are an important source of oxidative stress and have been shown to cause hypertrophic forms of cardiomyopathy in animal models. Furthermore, excess copper plays a pivotal role in Wilson’s disease, an important HCM differential diagnosis. Copper chelation, therapy in Wilson’s disease, has recently been demonstrated to reverse LHV and organ fibrosis in several animal disease models and humans with Type 2 diabetes. Surprisingly, there is no published data concerning copper homeostasis in patients with HCM. We investigated whether patients with HCM have overt abnormalities in copper and zinc homeostasis.

Methods: With ethical approval, we compared 20 randomly selected HCM patients from our local database with 16 matched healthy volunteers. Each participant provided 24 hour urine and fasting blood serum samples which were analysed for copper/ceruloplasmin/zinc using the highly sensitive and widely validated technique of Inductively Coupled Plasma Mass Spectrometry.

Results: HCM patients exhibited significantly higher levels of serum copper and zinc as compared to controls, but this did not reach statistical significance. However, analysis of variance showed that levels of copper were significantly lower in patients with the clinical phenotype of obstructive hypertrophic cardiomyopathy (n=12) than in those with non-obstructive disease (n=8) (p=0.016). Of all clinical and laboratory parameters tested, only mean arterial blood pressure was significantly lower in the obstructive subgroup (p=0.031). Zinc levels were also lower in obstructive disease compared to non-obstructive disease (p=0.042). No significant differences were found for zinc levels between any other groupings.

Conclusions: These findings suggest that HCM patients have altered copper and zinc homeostasis. This may contribute to the pathogenesis of the disease and provide further support for the consideration of therapy aimed at regulating copper metabolism for the treatment of HCM.
Conclusions: HCM patients exhibit overtly altered copper homeostasis. Coupled with the previous observation of LHV and fibrosis regression induced by copper chelation therapy these findings provide a mechanistic basis for copper chelation therapy to be tested in HCM.

**CARDIOMYOPATHIES: DIAGNOSIS**

**P4297 A French registry of takotsubo syndrome in non-academic hospitals (OFSETT)**


Purpose: Takotsubo syndrome remains the subject of investigation. We report on the management of and processes of care in consecutive patients with Takotsubo syndrome using data from a French registry (OFSETT).

Methods: Between November 2010 and December 2011, 15 non-academic hospitals with a high volume of percutaneous coronary procedures (>1000) included consecutive patients diagnosed with Takotsubo syndrome according to the Mayo clinic diagnostic criteria.

Results: A total of 121 patients were enrolled: 89% were women and the mean age was 72±12 years. Most of the women (89%) were >50 years old. 8% of patients had diabetes, 30% were current smokers and 52% had hypertension. Symptoms of Takotsubo syndrome were chest pain (81%), dyspnoea (27%), syncope (5%). The mean maximum troponin level was 7.8 ng/mL and the mean maximum B-type natriuretic peptide level was 1013 pg/mL. ECG showed a negative T wave in 73%, ST elevation in 42% and/or a new Q wave in 29%. In-hospital treatment included nitrates (11% of patients), unfractonated heparin (25%), low-molecular-weight heparin (79%), aspirin (91%), and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (75%). None of the patients died during hospitalization. At discharge, patients were treated with aspirin (99%), statins (96%), beta-blockers (75%), ACE/ARB (79%) and/or neurotropic agents (26%).

Conclusions: These observational data from 15 non-academic French hospitals provide insights into the characteristics of patients with Takotsubo syndrome and current processes of care for this population. Furthermore, they offer an opportunity for comparison with data from patients with acute myocardial infarction.

**P4298 Syncope in hypertrophic cardiomyopathy: the diagnostic role of flow mediated dilation**

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Introduction: Hypertrophic Cardiomyopathy (HCM) is an inherited myocardial disease characterized by unexplained increased left ventricular wall thickness associated with nondilated ventricular chambers in the absence of other cardiac or systemic disease. Syncope occurs in approximately 15–25% of patients with HCM. The principal causes can be arrhythmia and a primary haemodynamic mechanism. Abnormal blood pressure response during exercise and left ventricular outflow tract obstruction are the most important haemodynamic mechanisms.

Purpose: Administration of cardiotoxic anticancer agents results in a dose-dependent and significant increase in left ventricular mass (LVM). This study investigated if these agents can cause cardiac mechanisms that occur with this phenomenon in an effort to predict safe doses of anticancer agents.

Methods: A total of 229 consecutive patients with breast cancer (all females; mean age: 51±9 years) who completed adjuvant chemotherapy with three drugs (epirubicin, cyclophosphamide, and fluorouracil [CEF]) over a 60-month period were studied. Echocardiography was performed before and after several cycles of CEF.

**Conclusion:** The increased expression (on 43%) of TyrRS was revealed in total sera of 30 DCM patients with CHF, II-III functional NYHA classes, compared to control.

**P4296 Cardiotoxic anticancer agents induce an increase in myocardial weight: a pathophysiological study of ischemic cardiac mechanics**

M. ARAO, M. HANSSON, S. CATTAN, F. ALBERT, J.J. DUJARDIN, M. HANSSEN, S. CATTAN, F. ALBERT.

Purpose: Administration of cardiotoxic anticancer agents results in a dose-dependent and significant increase in left ventricular mass (LVM). This study investigated if these agents can cause cardiac mechanisms that occur with this phenomenon in an effort to predict safe doses of anticancer agents.

Methods: A total of 229 consecutive patients with breast cancer (all females; mean age: 51±9 years) who completed adjuvant chemotherapy with three drugs (epirubicin, cyclophosphamide, and fluorouracil [CEF]) over a 60-month period were studied. Echocardiography was performed before and after several cycles of CEF.

**Conclusion:** The increased expression (on 43%) of TyrRS was revealed in total sera of 30 DCM patients with CHF, II-III functional NYHA classes, compared to control.

**P4295 Tyrosyl-tRNA synthetase: peculiarities of myocardial synthesis and autoimmune reactions at dilated cardiomyopathy**


**Purpose:** Administration of cardiotoxic anticancer agents results in a dose-dependent and significant increase in left ventricular mass (LVM). This study investigated if these agents can cause cardiac mechanisms that occur with this phenomenon in an effort to predict safe doses of anticancer agents.

Methods and materials: Recombinant proteins full-size TyrRS and its N- and C-terminal modules isolated from the bacterial strains based on Escherichia coliBL21(DE3)pLysE. TyrRS expression in myocardium was identified by Western-blot analysis in pathomorphologic specimens of three DCM-affected human myocardia and samples of myocardium of three of them were studied in an effort to predict safe doses of anticancer agents. Antibodies (Abs) directed against ARSs are associated with different disease (myositis, arthritis, heart failure etc.). Moreover, the catalytic N-terminal module of tyrosyl-tRNA synthetase (TyrRS) may function as immunomodulating factor (similar interleukin-6) and C-terminal non-catalytic domain - as endothelial and monocyte activating polypeptide-like EMAP II. The aim of investigation was to study the expression of TyrRS in myocardium and to examine the peculiarities of autoimmune reactions against full-size TyrRS and its N- and C- terminal modules at dilated cardiomyopathy (DCM).

Results: The increased expression on 43% of TyrRS was revealed in total lysate and especially in nuclear subtraction of DCM-affected cardiomyocytes in compared to control. The increased level (for 29.3%) of IgG class anti-TyrRS antibodies against full-size TyrRS, against C-terminal module (for 18.5%) and C-terminal modules (for 65.5%) were found in blood serum of DCM patients, compared with healthy donors. The degrees of DCM sera IgM Abs elevation against full-size TyrRS and its isoforms were measured by ELISA method in sera of 30 DCM patients with CHF, II-III functional NYHA classes, chronically treated with beta-blocker, inhibitor ACE, diuretic. Sera of 20 healthy donors were examined as a control. To study the effect of anti-TyrRS, purified from DCM pts' sera with immunofluorescence chromatography, on TyrRS enzymatic activity we analyzed parameters changes of aminoacylation reaction of cognated tRNA catalyzed by TyrRS.

**Conclusion:** These results demonstrated a novel antigen-target at DCM - tyrosyl-tRNA synthetase and revealed its potential role at disease development.

**P4294 Serum caeruloplasmin levels were correlated with myocardial disease characterized by unexplained increased left ventricular wall thickness associated with nondilated ventricular chambers in the absence of other cardiac or systemic disease. Syncope occurs in approximately 15–25% of patients with HCM. The principal causes can be arrhythmia and a primary haemodynamic mechanism. Abnormal blood pressure response during exercise and left ventricular outflow tract obstruction are the most important haemodynamic mechanisms.**
The extent and consequences of diagnostic uncertainty in individuals assessed for arrhythmogenic right ventricular cardiomyopathy

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Purpose: The diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) is based on clinical findings. The findings of such tests can be non-specific in the early stages of the disease therefore long term follow up and serial testing are often necessary to make a definite diagnosis. The diagnostic criteria were revised in 2010 with the intention of increasing their sensitivity and specificity. Despite this there are individuals who can be given neither a definite diagnosis or reassurance because the manifestations of the disease are slow to develop. Relatives of affected individuals assessed as part of familial screening are particularly likely to fall into this category. Less than 50% of probands with ARVC have a identifiable pathogenic mutation, therefore genetic screening cannot resolve this problem. We constructed a registry of individuals who have been seen in the north of England for ARVC to determine how many individuals live with long term diagnostic uncertainty and the resources required for their ongoing follow up.

Method: Individuals seen by clinical services in connection with ARVC from 2005 to the present were identified retrospectively from clinical records. Major and minor diagnostic criteria for ARVC were identified from the results of clinical tests using the 2010 criteria.

Results: 92 individuals have been assessed for ARVC and found to have some clinical or genetic abnormality. 69 individuals (76%) lack a definite diagnosis. 21 are known to have a pathogenic mutation and were followed up to identify the existence of phenotypic features over time. Genetic screening was not an option for the remaining 48 individuals. The mean duration of follow up for this group was 5.4 years, SD4.5, range 1.1 to 21.1. For every 5 years of follow up individuals without a definite diagnosis had a mean of 3 echocardiographic examinations, 2 cardiac MRIs and 1 ambulatory ECG assessment.

Conclusions: The majority of individuals seen in clinical practice for suspected ARVC lack a definite diagnosis. These individuals live with diagnostic uncertainty of a potentially life threatening disease for many years and require regular clinical follow up and repeated clinical testing to reassess their phenotype. Our findings underline the importance of research to identify the clinical significance of mutations and the need for a novel diagnostic test for presumptively individuals.

In dilated cardiomyopathy the stimulating potential of anti-beta1-receptor autoantibodies is positively correlated with the depression of left ventricular function

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Dilated cardiomyopathy (DCM) characterized by progressive cardiac dilatation and dysfunction is one of the main causes of severe heart failure in younger adults. Previously we introduced a live cell assay for the detection of functional anti-beta1 receptor autoantibodies (beta1-aabs) using fluorescence resonance energy transfer (FRET) microscopy. Here we used this method to investigate the relationship between the receptor-activating potential of beta1-aabs and cardiac dysfunction in DCM.

Methods: The analyzed DCM population (n=97) had significant CAD excluded and was stable on medication according to current therapy guidelines for at least 3 months. In our outpatient-unit blood was drawn and immediately processed for autoantibody testing. All patients tested underwent echocardiography to assess left ventricular (LV) function, mean age 45±12 years, over a median follow-up of 36±7 months. First examination: all patients underwent a 12-lead ECG, a trans thoracic echocardiogram and MRI scan. Subsequently a clinical three-month follow-up was performed, during which the patients had undergone several 24-hour Holter monitoring and an exercise test using modified Bruce protocol. During follow-up all patients were submitted to endo-/exfoliation based cardiac MRI scans at baseline and after ischemia provoked by the arterial clamp.

Results: 10 (41.67%) patients on 24 had one or more syncopal episodes before and during follow-up whereas 14 (58.33%) patients never fainted. Patients with syncope and obstructive HCM showed a three times higher FMD (see Table 1).

Conclusions: Patients with HCM and sincope show abnormal peripheral dilatation (FMD). Our study suggests that only an extensive multidisciplinary investigation may be helpful to identify the mechanisms of syncope.
The impact of dynamic intraventricular obstruction on left ventricular mechanics in hypertrophic cardiomyopathy

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Background: LV twisting and untwisting are integral components of ventricular contraction, diastolic suction, and filling. In hypertrophic cardiomyopathy (HCM) myocardial fibres disarray, interstitial fibrosis and dynamic obstruction could influence left ventricular (LV) mechanics. Data regarding the impact of the dynamic LV outflow tract (LVOT) obstruction on LV mechanics are limited and discordant.

Purpose: To assess LV mechanics in patients (pts) with obstructive (HOCM) and non-obstructive (NHCM) HCM versus normal subjects.

Methods: We prospectively enrolled 35 pts (52 ±15 years, 16 men) with HCM (19 with HOCM and 16 with NHCM, according to the presence/absence of a dynamic LVOT gradient of > 30 mmHg) and 36 age- and gender-matched normal subjects (47 ±12 years, 12 men). Pts with apical HCM have been excluded. A comprehensive echocardiogram was performed in all. LV filling pressures were assessed using the E/e’ average ratio. Global longitudinal LV strain (GLS) and LV torsion parameters have been assessed by speckle tracking echocardiography. Peak basal and apical radial and torsion rates and contraction ratios were also measured. LV untwisting rate were determined. Time intervals from peak R wave (ECG) to each of them were measured and normalized to the RRI interval. Mitral regurgitation (MR) severity was graded from 1 to 4.

Results: Pts with HOCM were older (p =0.009) and had more severe MR (p =0.01) than pts with NHCM. There were no significant differences between HOCCM and NHCM pts regarding LVmass, E/e’, ratios, systolic and diastolic myocardial velocities, GLS and p=0.05 for all. Compared to normal subjects, pts with HOCM, unlike pts with NHCM, had higher values for apical LV rotation (21.7 ±8 vs 16 ±6.3, p =0.01) and basal rotation rate (p =0.00) basal UVrotation (p =0.04) and LV torsion (3.7 ±1.1 vs 2.8 ±0.8 °/min, p =0.002). Time to peak LV untwisting rate was statistically longer than in normal subjects in both HOCM and NHCM pts (p =0.001 and p =0.01, respectively). In pts, LV torsion was related to age (r =0.49, p =0.005), GLS (r =0.67, p =0.001), LVmass (r =0.42, p =0.01) and the presence of dynamic obstruction (r =0.38, p =0.02). In multivariate analysis LV torsion was independently correlated with GLS (p =0.05, p =0.03) and the presence of dynamic obstruction (p =0.35, p =0.04).

Conclusions: In pts with HCM, LVOT obstruction is related to changes in LV mechanics: increased apical and basal rotation, increased LV torsion, and delayed LV untwisting. Increased LV torsion is independently related to the presence of dynamic LVOT obstruction. These findings could provide new insights into the pathophysiology of HCM.

Cardiomyopathy in mitral valve prolapse

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Purpose: In some inherited connective tissue diseases with involving of the cardiovascular system, e.g. Marfan syndrome has been reported early impairment of contractility, diastolic suction, and filling. In hypertrophic cardiomyopathy (HCM) increased LV torsion is independently related to the presence of dynamic LVOT obstruction in HCM patients.

Methods: We prospectively enrolled 35 pts (52 ±15 years, 16 men) with HCM (19 with HOCM and 16 with NHCM, according to the presence/absence of a dynamic LVOT gradient of > 30 mmHg) and 36 age- and gender-matched normal subjects (47 ±12 years, 12 men). Pts with apical HCM have been excluded. A comprehensive echocardiogram was performed in all. LV filling pressures were assessed using the E/e’ average ratio. Global longitudinal LV strain (GLS) and LV torsion parameters have been assessed by speckle tracking echocardiography. Peak basal and apical radial and torsion rates and contraction ratios were also measured. LV untwisting rate were determined. Time intervals from peak R wave (ECG) to each of them were measured and normalized to the RRI interval. Mitral regurgitation (MR) severity was graded from 1 to 4.

Results: Pts with HOCM were older (p =0.009) and had more severe MR (p =0.01) than pts with NHCM. There were no significant differences between HOCCM and NHCM pts regarding LVmass, E/e’, ratios, systolic and diastolic myocardial velocities, GLS and p=0.05 for all. Compared to normal subjects, pts with HOCM, unlike pts with NHCM, had higher values for apical LV rotation (21.7 ±8 vs 16 ±6.3, p =0.01) and basal rotation rate (p =0.00) basal UVrotation (p =0.04) and LV torsion (3.7 ±1.1 vs 2.8 ±0.8 °/min, p =0.002). Time to peak LV untwisting rate was statistically longer than in normal subjects in both HOCM and NHCM pts (p =0.001 and p =0.01, respectively). In pts, LV torsion was related to age (r =0.49, p =0.005), GLS (r =0.67, p =0.001), LVmass (r =0.42, p =0.01) and the presence of dynamic obstruction (r =0.38, p =0.02). In multivariate analysis LV torsion was independently correlated with GLS (p =0.05, p =0.03) and the presence of dynamic obstruction (p =0.35, p =0.04).

Conclusions: In pts with HCM, LVOT obstruction is related to changes in LV mechanics: increased apical and basal rotation, increased LV torsion, and delayed LV untwisting. Increased LV torsion is independently related to the presence of dynamic LVOT obstruction. These findings could provide new insights into the pathophysiology of HCM.

Prevalence of psychiatric disorders in Tako-Tsubo cardiomyopathy

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Purpose: Tako-Tsubo cardiomyopathy (TTC) involves transient left ventricular dysfunction, generally subsequent to stress. Most often, it affects postmenopausal women. Unusual prevalence of psychiatric disorders has been forwarded as an explanation of the deleterious and disproportionate catecholergic response to stress. However, this prevalence has never been clearly established. The aim of our study was to determine the prevalence of psychiatric disorders in TTC.

Methods: A history of psychiatric problems and psychotropic treatment were examined prospectively in a population of 70 TTC patients recruited over 36 months in 3 hospital centers. These were compared with those of 53 anterior ST-segment elevation myocardial infarction (STEMI) and 51 anterior non-ST-segment elevation myocardial infarction (NSTEMI). These groups were matched for age and gender.

Results: Close on 61.4% of TTC presented a history of psychiatric problems versus 28.4% for ACS (p <0.001), i.e. 2.16-fold more. The most frequently encountered psychiatric disorders in TTC were anxiety (30%), depression (30%) and schizophrenia (3.2%). Long-term psychotropic treatment had been delivered to 48.7% of TTC patients versus 20.1% for ACS (p <0.001). The most commonly used psychotropic treatments in TTC were: benzodiazepines (27.1%), selective serotonin reuptake inhibitor (20%), neuroleptics (7.1%) and other anxiolytics (7.1%). The mean number of psychotropics per patient was 0.78 in TTC and 0.28 in ACS (p <0.001), i.e. 2.79-fold more. In our series, TTC were also three times more often with chronic respiratory insufficiency (24.6% versus 9.6%, p=0.008) and cancer (21.7% versus 6.7%, p=0.004), pathologies which are often associated with anxiety and depression disorders.

Conclusion: The prevalence of psychiatric disorders in TTC is strong, as witnessed by the high intake of psychotropic treatments. Anxiety-related and depressed disorders are most often at issue. The observed elevated presence of cancer and chronic respiratory insufficiency could be partly responsible for these disorders.

Clinical characteristics and short-term outcome of patients with Tako-tsubo syndrome and critical coronary stenosis: comparison with patients with Tako-tsubo with normal coronary arteries

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Purpose: Tako-tsubo syndrome (TTS) may be associated with significant coronary artery disease (CAD), but the prevalence, clinical characteristics and outcomes of TTS with CAD and the pathogenic role of CAD are not well defined. The aim of the study was to compare the clinical characteristics and short-term outcome of pts with TTS and critical CAD with those with TTS with no CAD and no critical CAD.

Methods and Results: 184 consecutive pts (aged 71 ±12 yrs, 90% women) admitted with acute symptoms and ST-T changes who showed a reversible pattern of ST elevation myocardial infarction (NSTEMI) and 51 anterior non-ST-segment elevation myocardial infarction (STEMI) and 51 anterior non-ST segment elevation myocardial infarction (STEMI) were compared with those of 53 anterior STEMI and 51 anterior NSTEMI. These groups were matched for age and gender.

Results: In pts with TTC and critical CAD with those with TTC vs without only 38% had a previous history of CAD (p =0.001), i.e. 2.16-fold more. In our series, TTC were also three times more often with chronic respiratory insufficiency (24.6% versus 9.6%, p=0.008) and cancer (21.7% versus 6.7%, p=0.004), pathologies which are often associated with anxiety and depression disorders.

Conclusion: The prevalence of psychiatric disorders in TTC is strong, as witnessed by the high intake of psychotropic treatments. Anxiety-related and depressed disorders are most often at issue. The observed elevated presence of cancer and chronic respiratory insufficiency could be partly responsible for these disorders.
Completely autologous biotube vascular grafts: eosin
Angiotensin II inhibits ecSOD and ATP7A and
as an instant regenerative medicine.

Methods and Results: Micropored acrylic tubes (diameter: 4 mm, length: 4 cm, pore size: 0.5 mmf) filled with a PBS solution of agar (0.3%) including eosin Y and main consisting of collagen and fibroblasts, with extremely thick wall (thickness: 0.5–1 mm) and rich angiogenesis were obtained. Their elastic modulus was similar to that in the native arteries.

Conclusion: Only 1-week preparation of BIOTUBE vascular grafts with thick wall in surgical handling between the biotubes and native arteries. After blood circulation in the carotid arteries using standard microsurgery. There were no major discrepancies in surgical handling between the biotubes and native arteries. After blood circulation was re-established, periodic cycles of inflation and deflation of the grafts were noted.

Conclusions: We demonstrated that TLR4 plays an important role in regulating the temporal and spatial distribution of MAC subtypes during arteriogenesis in a rat and mouse model was investigated.

Methods: Rats (n=42) were subjected to FAL and shunting of the femoral artery with the accompanying vein distal to the ligature. Local MAC-subpopulations were histologically phenotyped using CD68 (ubiquitous macrophage marker) and CD163 (M2-MAC marker) during arteriogenesis. Whereas M1-MAC are detected adjacent to the media, M2-MAC are present in the outer perivascular region of collateral vessel. In mice the distribution of MAC within collateral vessel did not reflect the composition of circulating monocytes. However, suppressing inflammatory monocytes (M1) with DEX prevented the elevated M2-MAC recovery (36.7±6.1% vs. 61.9±5.9% in sham controls; n=5; p<0.005), whereas IL10 application significantly increases perfusion (81±5.5%; n=5; p<0.05).

Conclusion: The distinct early increase and spatial distribution of M2-MAC support the idea that this subtype plays a predominant role during collateral remodelling. This investigation demonstrates that a forced shift towards M2-MAC improves the arteriogenic response.

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Angiotensin II inhibits ecSOD and APTP7A and upregulates oxidative stress via toll-like receptor 4

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Aims: Toll-like receptor 4 (TLR4) and angiotensin II (AngII) involve the production of reactive oxygen species (ROS) in the vascular wall. AngII has been shown to increase antioxidant enzyme extracellular superoxide dismutase (ecSOD) and copper transporter APTP7A. However, the role of TLR4 in AngII-induced ROS production on the regulation of ecSOD remains unknown.

Methods: TLR4-deficient (TLR4-/-) and wild-type (WT) mice were subjected to pressure overload by AngII or norepinephrine (NE). We also examined the effects of AngII receptor type 1 (AT1) receptor antagonist irbesartan in AngII-induced hypertension. Systolic blood pressure (BP) and wall-to-lumen (W/L) ratio were measured. ROS content was assessed with fluorescent DHE staining. The expression of ecSOD was measured by Western-blot analysis.

Results: BP and W/L ratio compared with that in the untreated mice (3.6±1.9 vs. 0.9±0.8 in sham controls; n=18). At later time points (3d, 7d, 14d, 28d) both subpopulations further increased in number. In HFD-mice, the proportion of the perivascular space (14d: M2:37.5±6.9 and M1: 28.1±16.0 vs. 19±4; p<0.05) compared to that in the control mice (14.9±3.9 pos. cells/vessel, n=18), was increased. The local distribution of the subpopulations changes during the arteriogenic process. Whereas M1-MAC are detected adjacent to the media, M2-MAC are present in the outer perivascular region of collateral vessel. In mice the distribution of MAC within collateral vessel did not reflect the composition of circulating monocytes. However, suppressing inflammatory monocytes (M1) with DEX prevented the elevated M2-MAC recovery (36.7±6.1% vs. 61.9±5.9% in sham controls; n=5; p<0.005), whereas IL10 application significantly increases perfusion (81±5.5%; n=5; p<0.05).

Conclusion: The distinct early increase and spatial distribution of M2-MAC support the idea that this subtype plays a predominant role during collateral remodelling. This investigation demonstrates that a forced shift towards M2-MAC improves the arteriogenic response.
Saphenous vein aorto-coronary bypass graft arteriosclerosis in patients with chronic kidney disease: more clarification, but less vasoconstrictor potential

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Purpose: Atherosclerotic coronary artery lesions are more calcified in patients with than without chronic kidney disease (CKD). Day 10 of the development of calcification in arteries is determined by calcium deposition. Using a bioassay of rat mesenteric arteries with intact (+E) and denuded (-E) endothelium, the vasoconstrictor response to coronary aspirate plasma was quantified and normalized to that by potassium chloride (KClmax = 100%).

Methods: In patients with and without CKD (n=20/20), SVG calcium fog was determined from virtual histology using intravascular ultrasound analysis before stent implantation. Coronary arterial blood was retrieved during stent implantation and divided into particulate debris and plasma. The calcium concentration of particulate debris was determined by flame atomic spectrophotometry. The concentrations of calcium, magnesium, and trace elements were determined.

Results: There was more dense calcium in patients with than without CKD (15.3±3.3 vs. 3.1±1.1% of plaque volume). Patients with CKD had more particulate debris and aortic calcium release than patients without CKD. In contrast, the release of calcium from coronary blood was increased.

Conclusion: Graft arteriosclerosis in patients with CKD is more calcified, but the aspirate has surprisingly less serotonin and vasoconstrictor potential.

The effect of treatment with drospirenone/ethinyl estradiol alone or in combination with metformin on elastic properties of aorta in women with polycystic ovary syndrome

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Background: Polycystic ovary syndrome (PCOS) is a heterogeneous clinical condition. Oral contraceptive pills (OCPs) have conventionally been the mainstay of treatment for the amelioration of the metabolic derangements and menstrual cycles in women with PCOS. Metformin has beneficial effects on insulin resistance and endothelial functions. To our knowledge, the effect of metformin/OCP combination treatment on aortic stiffness has not been studied so far.

Objective: The aim of this study was to investigate the effects of treatment with drospirenone/ethinyl estradiol (EE/E2) alone or in combination with metformin on the elastic properties of aorta in women with PCOS.

Methods: Thirty-seven women with PCOS patients (mean age 23.1±5.0) randomized to oral treatment of alone OCP (n = 19) or OCP combination with metformin (n = 18) for 6 months. The elastic parameters of aorta: ‘aortic strain’, ‘aortic distensibility’, ‘aortic diameter alteration’, and ‘aortic stiffness index’ have been calculated by appropriate formulae. The hormonal profile, HOMA-IR score, basal insulin and glucose levels were studied in both groups. Before and after 6 months treatment, echocardiographic measurements and laboratory tests were also obtained.

Results: After 6 months treatment, significant weight loss and decrease in BMI were observed in the metformin group (75.3±13.3 kg to 72.9±13.5 kg and 31.7±7.3 kg/m² vs. 30.4±7.3 kg/m², p = 0.001 and p = 0.001, respectively). Conversely in the yazine group, increases in BMI and weight were observed (68.8±18.3 kg to 71.6±21.2 kg, and 26.4±6.2 kg/m² to 27.4±6.9 kg/m², p = 0.159 and p = 0.149, respectively). There were increases in aortic strain and distensibility (7.7±4.2 to 7.8±3.6 and 7.2±4.1 to 7.7±3.6, p = 0.926 and p = 0.593, respectively) and decreases in the stiffness index in the yazine group but these were not significant (8.8±7.4 to 8.2±6.6, p = 0.772). In the metformin group, adjusted values of aortic stiffness index decreased significantly at 6 months follow-up (10.0±2.5 to 7.0±3.0, p = 0.021 and aortic distensibility and strain increased but not significantly (7.0±3.4 to 9.3±3.9 and 6.8±3.9 to 9.4±3.5, p = 0.163 and p = 0.071, respectively) at 6 months follow-up.

Conclusion: We demonstrated an improvement in the elastic parameters of aorta by adding metformin to OCP treatment. Additionally, a reducing in testosterone levels correlated with a reduction in aortic stiffness hence may be beneficial for cardiovascular risk. These results indicate that metformin plus OCP treatment may decrease cardiovascular disease risk in women with PCOS.

Comparison of microparticle counts in patients with acute coronary syndrome patients with two methodologies

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Background: Circulating microparticles (MPs) are increased in cardiovascular disease and have become promising biomarkers in many pathological situations. Measurement of plasmatic MPs is not standardized and most studies have focussed on relatively large MPs due to technological limitations. We following compared two flow cytometric methodologies for the enumeration and characterization of MPs in acute coronary syndrome (ACS) patients and its changes during 30 days.

Methods: We recruited 113 ACS patients (aged 68±12 years, 65% males); sodium citrate platelet poor plasma was collected within 24 h of percutaneous coronary intervention (PCI). Day 0 samples were processed for the detection of coronary sinus blood platelet traps (PSMs). Day 10 samples were used to assess the potential for core vascular injury. MPs were measured using a FACSCalibur FCM, mainly PMPs (p=0.005). However no changes were detected in MPs counts following PCI (<PMPs = 0.51, EMPs = 0.40, MMPs = 0.24). When small-size MPs (0.1-0.5 μm) were quantified in a high sensitive FCM, a significant increase in pMPs and EMPs (p<0.012 and p<0.005, respectively) was found during the follow-up period (Table), but MMPs remained constant (p=0.91).

Conclusion: Latest generation of FCMS likely display higher sensitivity for MPs, mainly due to lower detection limits and background noise. The size of polychemose be not comparable to biological size of MPs, but conventional FCMS might not reliably detect MPs. In the search of MPs as potential biomarkers, technological improvements should not be underestimated.

Fibrin-related thrombosis risk in type 2 diabetes: relationship with vascular pathology and drug therapy

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Purpose: The formation of a platelet-rich fibrin clot represents the final step in the atherothrombotic process and the structure of the fibrin network determines predisposition to vascular ischaemia. Our aim was to investigate the effects of vascular disease, metabolic factors and drug therapy on clot structure/fibrinolyis.

Methods: A total of 875 participants of the Edinburgh type 2 Diabetes Study [age 68 (range 60-75) years, 450 males] were recruited and five parameters of clot structure/fibrinolysis were assessed using a dynamic ex vivo turbidimetric assay and confocal microscopy.

Results: Female gender was associated with longer clot formation time compared with males (562±6 vs 516±7 seconds, respectively; p<0.001), which may be related to higher maximum absorbance (0.37±0.005 vs 0.34±0.005, respectively; p<0.001) and/or impaired clot lysis time (803±20 and 665±12 seconds, respectively; p<0.001). Gender differences were confirmed by confocal microscopy and were still evident after adjusting for fibrinogen and plasmaing activator inhibitor (PAI-1) plasma levels. Age was associated with denser clots in men with a paradoxical enhancement in fibrinolysis, possibly related to lower PAI-1 levels. Male subjects with coronary artery disease had higher clot maximum absorbance in the presence of PAI-1.
Molecular mechanism of tissue factor regulation through RAGE-MT1-MMP axis in HMGB-1 stimulated-endothelial cells

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Backgrounds: The atherosclerosis is understood as a blood vessel inflammation. HMGB-1 is one of the mediators released from necrotic cells or macrophages that receives inflammatory stimuli. It plays a key role in the systemic inflammation. Tissue factor (TF), a physiological initiator of coagulation cascade, is known to lead to inflammation which promotes the thrombus formation in the onset of acute coronary artery disease. We recently have shown that silencing of membrane type 1 MMP (MT1-MMP) suppressed the advanced glycation endproducts (AGE) triggered TF protein expression and phosphorylation of NF-κB in smooth muscle cells. These results suggest that MT1-MMP also relates to inflammatory conditions in vascular wall. However, it is still unclear about the association of HMGB-1 and MT1-MMP mediated TF expression. In this study, we investigated the molecular mechanism of TF expression in response to HMGB-1 stimulation and the involvement of MT1-MMP in endothelial cells.

Methods: Cultured human aortic endothelial cells were stimulated with 50µg/ml HMGB-1. The protein levels of TF and phosphorylated NF-κB were determined by Western blotting. The MT1-MMP activity was measured by ELISA. MT1-MMP expression was silenced by small interfering RNA (siRNA). GTP-loading of RhoA and Rac1 was assessed by pull-down assays.

Results: HMGB-1 increased MT1-MMP activity and activated small GTP binding protein RhoA and Rac1 within 5 minutes in endothelial cells, which was inhibited by silencing of receptor for AGE (RAGE) or MT1-MMP. TF protein expression was regulated by RhoA activation as well as Rac1 dependent NF-κB phosphorylation in HMGB-1 stimulated endothelial cells. siRNA to RAGE or MT1-MMP suppressed NF-κB phosphorylation and TF protein expression mediated via RhoA and Rac1 activation induced by HMGB-1.

Conclusion: We clarified that RAGE/MT1-MMP axis modified the HMGB-1 mediated TF expression thorough the RhoA and Rac1 activation and NF-κB phosphorylation in endothelial cells. These results suggested that MT1-MMP was involved in vascular inflammation and might be a good target for treating acute coronary syndrome.

Pharmacokinetic interactions between clopidogrel and rosuvastatin: effects on vascular protection in subjects with coronary heart disease


Background/Objectives: Genetic polymorphisms in the hepatic cytochrome P450 (CYP2C19) affect the antiplatelet effects of clopidogrel. Rosuvastatin is partially metabolized by the same cytochrome. We hypothesized that pharmacokinetic interactions between these drugs might affect their individual responses on vascular protection.

Methods: Patients with stable coronary heart disease (N=20) were submitted to four consecutive 1 wk therapeutic regimens: aspirin, rosuvastatin 40 mg, rosuvastatin 40 mg plus clopidogrel 75 mg, or clopidogrel 75 mg alone. A loading dose of 300 mg clopidogrel was given in the first day. Biochemistry, platelet function (multiplex platelet analyzer), flow-mediated dilation (ultrasound of the brachial artery), endothelial progenitor cells, and microparticles (flow-citometry) were assessed at baseline and after 1 and 4 weeks. The MT1-MMP activity was measured by ELISA. MT1-MMP expression was silenced by small interfering RNA (siRNA). GTP-loading of RhoA and Rac1 was assessed by pull-down assays.

Results: Remarkable changes on LDL-cholesterol levels after 1 wk of statin therapy (-39%) as well as after 1 wk of its withdrawal (+61%) were observed. Clopidogrel (300 mg) increased the area under the curve from 0 to the last detectable concentration (AUClast, p<0.001) and the maximal concentration (Cmax, p<0.011) of rosuvastatin, but there was modest interaction with clopidogrel 75 mg. Clopidogrel concentrations were not affected by rosuvastatin. Rosu-

vastatin did not reduce the effectiveness of in vitro platelet aggregation inhibition by clopidogrel. However, the amount of plasma platelet microparticles increased after withdrawal of rosuvastatin, despite continuous clopidogrel therapy. Remarkable improvement in the flow-mediated dilation was observed 1 h after rosu-

vastatin initiation, and it was not affected by concomitant clopidogrel therapy or related to the circulating endothelial progenitor cells.

Conclusions: This study shows beneficial pharmacokinetic interaction between clopidogrel and rosuvastatin that seems to extend the vascular protection provided by each drug alone, highlighting the importance of the combined therapy for subjects with coronary heart disease.

Endothelial progenitor cells in relation to endothelin-1 and endothelin receptor blockade: a randomized controlled trial


Aims: Endothelial progenitor cells (EPC) represent an endogenous repair mechanism involving reendothelialization and neangiogenesis. Patients with both diabetes and vascular disease associated with endothelial dysfunction have low numbers of circulating EPC. The endothelin-derived peptide, endothelin-1 (ET-1), is increased in patients with type 2 diabetes and vascular complications. ET-1 has been suggested to contribute to endothelial dysfunction in this condition. Therefore, we investigated the relation between EPC and plasma ET-1 and the effects of dual ET-1 receptor antagonism on the number of EPCs.

Methods: In this double blind study patients with type 2 diabetes mellitus and microalbuminuria were randomized to treatment with the dual ETA/ETB receptor antagonist bosentan treatment (125 mg bid, n=17) or placebo (n=19) for four weeks. Different EPC subpopulations were enumerated by flow cytometry using three staining (CD34, CD133, kinase domain receptor, KDR) at baseline and at the end of treatment. Viability was assessed by 7AAD and Annexin V-staining.

Results: Baseline ET-1 levels correlated significantly with C-reactive protein levels. Patients with ET-1 levels below the median had higher levels of CD34+CD133+ and CD34+KDR+ (Table 1). There was no difference in markers of EPC apoptosis or circulating markers of endothelial damage between patients with ET-1 levels below or above the median. Four weeks treatment with bosentan did not change EPC levels.

Soluble adenylyl cyclase controls oxidative stress-induced apoptosis of smooth muscle cells

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Apoptosis of vascular smooth muscle cells (VSMC) in advanced atherosclerotic plaques is an important cause of plaque instability and may result in plaque rupture followed by thrombosis and sudden death. Within several pro-apoptotic factors, enhanced reactive oxygen species generation has been suggested as a cause for VSMC death and plaque instability. However, the precise mechanism of oxidative stress-induced VSMC apoptosis is still poorly understood. The involvement of sAC in apoptosis of VSMC was the aim of the present study. For this purpose, apoploietic agonists were used and the siRNA to this cyclase, mammalian cells possess a second source of cAMP, the ubiquitin-
The p110alpha subunit of PI 3-kinase is crucially involved in neointima formation by mediating smooth muscle cell proliferation and survival.

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The proliferation, migration and survival of vascular smooth muscle cells (SMCs) are essential for the neointima formation following balloon angioplasty. In this context, growth factors such as platelet-derived growth factor (PDGF) that activate receptor tyrosine kinases (RTKs) play a significant role, RTK's receptor-responses are largely mediated by activation of phosphatidylinositol 3'-kinase (PI3K).

Previously, we were able to demonstrate that in vitro inhibition of the catalytic PIK isoforms (p110alpha and p110beta) completely abrogated the growth factor mediated proliferation of SMCs. With the help of SMC-specific p110alpha deficient mice (p110alpha ko) we analysed in vivo the relevance of p110 alpha in restenosis formation following balloon angioplasty. The extent of neointima formation was quantified by following balloon angioplasty of carotid arteries in wild-type (WT), p110alpha ko and in heterozygous animals. In addition, we isolated aortic SMCs from these mice and analysed growth factor-mediated cellular proliferation, migration and apoptosis using BrdU incorporation assay (proliferation), modified Boyden-chamber (chemotaxis) and nucleosome ELISA (apoptosis).

PDGF-BB (30 ng/ml) induced proliferation (x-fold increase compared to unstimulated controls, n=3) of WT SMCs, proliferation of p110alpha ko SMCs (1.90±0.18) and heterozygous cells (3.49±0.28) was significantly reduced (p < 0.05). Likewise, PDGF (30 ng/ml) induced chemotaxis (x-fold increase ± s.e.m., n = 3) of WT SMCs (6.28±0.63). The migration of p110alpha ko SMCs (2.44±0.18) and heterozygous SMCs (3.36±0.41) was also significantly (p < 0.05) reduced compared to WT SMCs. Application of PDGF significantly reduced H2O2 (25 μM) induced apoptosis of WT SMCs by 30% ± 14% (n=4) whereas PDGF had only poor effects on H2O2 induced apoptosis of heterozygous SMCs (22% ± 19%, n=4, not significant) and p110alpha ko SMCs (0% ± 13%, n=3, not significant). In conclusion, our results indicate that the p110alpha subunit of PI3K, is crucial for growth factor-mediated proliferation, migration and survival of SMCs in restenosis following balloon angioplasty. Therefore, p110alpha represents a promising therapeutic target.

VASCULAR BIOLOGY II

Neutrophils contribute to DVT formation by forming procoagulant and prothrombotic neutrophil extracellular traps

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Objective: Neutrophils have been primarily implicated in host defence, but it is increasingly recognised, that they also contribute to coagulation. One mechanism how they could do that is exposure of Neutrophil extracellular traps (NETs). These extracellular DNA structures have been found in deep venous thrombosis (DVT), but how they participate in thrombus formation in vivo is unclear. In this study we wanted to assess the dynamics of NET formation in vivo and their impact on DVT development in a murine flow reduction model of the inferior vena cava (IVC).

Methods: Thrombosis was induced in C57Bl6 mice by placing a narrowing figure around the IVC, resulting in a reduction of blood flow velocity (n=16). NET formation in vivo was visualised by intravital 2-photon microscopy. Thrombogenesis and NET formation were quantified in Gpiib−/−, Dnase and hepatared animals (n=7 each). The ability of NETs to bind and activate factor XII was assessed in vitro.

Results: Neutrophils were recruited very early after initiation of flow reduction in the IVC, supported by platelets. NET formation in the IVC, triggered by platelets, could be detected in vivo as early as 3h after flow reduction. We found that NETs were binding platelets, tissue factor, and fibrinogen, demonstrating a concentration of procoagulatory and prothrombotic factors on their surface. This is highlighted by the fact that coinubcation of activated platelets and neutrophils resulted in significant FXII activation. Inhibition of NETs by an antibody directed against the H2A-H2B-DNA complex significantly attenuated FXII activation. The functional impact of NETs for DVT formation is indicated by the finding that disruption of NETs by DNase treatment resulted not only in a reduced number of NETs, but also in a markedly reduced thrombus weight compared to wt control. Surprisingly, injection of heparin resulted in a diminished number of NETs inside the IVC, which could add to its antithrombotic effect (n=3).

Conclusion: Here we show that neutrophils contribute to DVT by NET formation, which is triggered by adhered platelets. This provides a platform for platelet adhesion and concentration of procoagulatory factors on their surface, linking inflammation and thrombosis at the cellular level. Thus, disruption of NETs could be an interesting new therapeutic approach for prophylaxis and treatment of DVT.
in mMPs during the follow-up period. MP levels 30 days after STEMI were not different from values seen in stable CAD (p=NS).

On linear regression analysis, AnV-MP levels were negatively associated with TPA levels on day 1 (p=0.01), mMPs and pMPs were also associated with lower TAFI levels on day 30 (p=0.013 and p=0.016, respectively).

**Conclusion:** Small-size eMPPs and apoptotic MPs are significantly down-regulated on admission with STEMI, possibly due to their increased consumption by thrombus/damaged myocardium. Different types of MPs are linked to parameters of the fibrinolytic system. These findings indicate pathophysiological roles for small-size MPs in STEMI and may potentially become therapeutic targets.

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**P4323**

Leptin is expressed in human carotid atherosclerotic plaques and plays an active role in plaque stability via its effects on human vascular smooth muscle cells phenotype

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**Purpose:** Leptin is assumed to contribute to the pathogenesis of atherosclerosis, through interaction with its receptor OβR on vascular cells. However, no quantitative data on its expression in human plaques have been reported so far and its impact on plaque vulnerability remains unclear. In the present study, we investigated this link in patients with carotid artery disease and hypothesized that leptin could play an active role in this process via its effects on human vascular smooth muscle cells (VSMC), promoting redox signalling.

**Methods:** Carotid plaque specimens were collected from 60 patients undergoing carotid endarterectomy. Each sample was evaluated by ELISA and qPCR for leptin and OβR expression, by histology and immunohistochemistry for detection of leptin, OβR, VSMC, collagen, macrophages, cell proliferation (Ki67) and by Western Blot for ERK signaling pathway mediating cell migration and proliferation. The effects of leptin (0-100 ng/mL) on human VSMC migration, proliferation, collagen synthesis and ERK signaling were investigated in cell culture.

**Results:** leptin and its receptor are co-localized with plaque VSMCs by immunofluorescence. Intraplaque leptin was correlated, negatively with plaque macrophage content (p-0.0001, r=0.645) and positively with plaque stability index (collagen to macrophage area ratio) and VSMC content (p=0.0006, r=0.5; p<0.0014, r=0.615, respectively). Plaque leptin was positively correlated with plaque ERK signaling activation (p=0.01, r=0.697), and tended to be correlated with VSMC proliferation index (% of Ki67 positive VSMC) (p=0.07). No similar correlation was observed concerning plaque OβR and leptin/OβR mRNA relative expression. Human VSMCs were exposed for 6 hours to leptin at low concentrations (0 to 20 ng/mL), a strong signal of migration and collagen production were observed, followed by a signal of proliferation at 72 hours at higher concentrations (0.2-100 ng/mL) with a maximum effect at 76 ng/mL. Interestingly, ERK activation in leptin stimulated VSMC (for 6 hours) was maximum at the concentration of 20 ng/mL, corresponding to its maximum effect on VSMC migration. ERK activation was also maximum in leptin stimulated VSMC, at the concentration of 75 ng/mL, for 72 hours, corresponding to leptin maximum effect on VSMC proliferation.

**Conclusions:** These results, for the first time, suggest that leptin could actively contribute to carotid plaque stability via various effects on human VSMCs.

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**P4324**

Endothelial Microparticles (EMP) are taken up in an Annexin I/PSR dependent pathway by target cells and promote endothelial regeneration

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**Background:** Activation and apoptosis of endothelial cells, key steps in the development of atherosclerosis, trigger the release of EMPs. The role of EMP in the progression of atherosclerosis is still unclear. Here, we present evidence that EMP influence endothelial-regenerating cells and promote recruitment/survival signals important for endothelial regeneration.

**Methods and results:** EMP were generated after starvation of human coronary endothelial cells (HCAEC) anisoidated by ultracentrifugation. Flow cytometry analysis and electronmicroscope was used to characterize size (<1 μm) and cellular origin of EMP. To test the effects of EMP in vivo and in vitro experiments were performed. Invivo, reendothelialization in mice after carotid injury was improved after pretreatment with EMP injection (29.8% vs. 50.7% remained denuded area, p<0.05). EPC level in blood, bone marrow and spleen were significantly increased in EMP-treated mice. In vitro, EMP promoted differentiation of monocellular cells into early outgrowth EPC (58.3% vs. 39%, p<0.05), protected target cells against apoptosis, and accelerated migration of HCAEC (59% vs. 43%, p<0.05). We next demonstrated EMP uptake by target cells (HCAEC, early EPC, late EPC). Following experiments were performed to investigate a possible uptake mechanism. Proteomic analysis and Western Blot revealed expression of Annexin I on EMP. Additional Western Blot analysis showed expression of PSR on target cells. siRNA experiments showed that the uptake of EMP by HCAEC was an Annexin I/Phosphatidylserine/receptor (PSR) dependent pathway. Furthermore, inhibition of Annexin I and PSR expression using siRNA inhibited EMP-mediated protection respectively, values normalized to TBP mRNA, n=6; p<0.001.

**Conclusion:** EMP induces signals of endothelial replenishment in vivo and in vitro. The Annexin I/PSR dependent pathway was identified as a crucial mechanism for EMP uptake by target cells.

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**P4325**

Lack of JunD promotes oxidative stress-induced vascular aging

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**Purpose:** Enhanced production of reactive oxygen species (ROS) is the major determinant of age-related endothelial dysfunction. JunD, a member of the activator protein 1 family of transcription factors, promotes redox homeostasis. We investigated the role of JunD in aging-associated endothelial dysfunction.

**Methods:** Endothelium-dependent relaxation to acetylcholine (Ach, 10-9-10-6mol/L) was assessed in aortic rings from young (6 months old) and old (22 months old) mice JunD+/− and wild-type (WT) mice. Nitric oxide (NO), superoxide anion (O2−) and peroxynitrite (ONOO−) were measured with electrochemical nanosensors at the surface of a single endothelial cell of mouse aorta. siRNA-mediated knockdown of JunD was performed in human aortic endothelial cell (HAECl) using lipofectamine. In healthy young (<30 years) and old (>60 years) subjects JunD gene expression was assessed in peripheral blood mononucleated by RT-PCR.

**Results:** In WT mice, age-dependent impairment of endothelium-dependent relaxation to Ach was associated with a reduction of age-matched WT animals (max relaxations: 51±4.8 (young) and 31±5.3 (old) vs age-matched group). Impaired response to Ach was restored by superoxide dismutase (SOD) and catalase, suggesting a ROS-mediated endothelial dysfunction in JunD−/− mice. Accordingly, enhanced NO breakdown and increased aortic O2− and ONOO− levels were already present in young JunD−/− mice. ROS scavenging enzymes manganese SOD and aldehyde dehydrogenase-2 were both downregulated in JunD−/− mice. Instead, p47phox NADPH oxidase subunit was increased. Expression of endothelial NO synthase (eNOS) was significantly reduced in JunD−/− mice. Surprisingly, in young (passage 5) and old (passage 15) HAECl we observed a similar age-dependent decrease in JunD gene expression paralleled by age-induced increase in O2− levels. Specific siRNA-mediated knockdown of JunD in young HAECl lead to increased O2− levels resembling those of old HAECl. Furthermore, JunD gene expression was decreased in peripheral monocytes from old compared to young healthy subjects (57.5±3.7 vs 113±6.7, respectively, p<0.001)

**Conclusions:** Aging-induced oxidative stress and endothelial dysfunction were markedly accelerated in JunD−/− mice compared with age-matched WT littermates. Moreover, JunD may be a crucial modulator of ROS-mediated human vascular aging, representing a novel molecular target for vascular disease prevention.

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**P4326**

Impaired periaortic adipocyte differentiation in angiotensin AT1 receptor deficient mice: Possible role in pro-inflammatory phenotypic modulation of perivascular adipose tissue

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**Background:** The angiotensin II type 1 (AT1) receptor in visceral white adipose tissue (WAT) is closely implicated in lipid metabolism and energy homeostasis.

**Abstract:** AT1−/− mice showed blunted vasorelaxation compared with age-matched WT animals (max relaxations: 51±1.5/83±3.4 (young) and 34±2.3 vs 58±2.4 (old) for JunD−/− and WT mice, respectively, n=6, p=0.05 vs age-matched group). Impaired response to Ach was restored by superoxide dismutase (SOD) and catalase, suggesting a ROS-mediated endothelial dysfunction in JunD−/− mice. Accordingly, enhanced NO breakdown and increased aortic O2− and ONOO− levels were already present in young JunD−/− mice. ROS scavenging enzymes manganese SOD and aldehyde dehydrogenase-2 were both downregulated in JunD−/− mice. Instead, p47phox NADPH oxidase subunit was increased. Expression of endothelial NO synthase (eNOS) was significantly reduced in JunD−/− mice. Surprisingly, in young (passage 5) and old (passage 15) HAECl we observed a similar age-dependent decrease in JunD gene expression paralleled by age-induced increase in O2− levels. Specific siRNA-mediated knockdown of JunD in young HAECl lead to increased O2− levels resembling those of old HAECl. Furthermore, JunD gene expression was decreased in peripheral monocytes from old compared to young healthy subjects (57.5±3.7 vs 113±6.7, respectively, p<0.001)

**Conclusions:** Aging-induced oxidative stress and endothelial dysfunction were markedly accelerated in JunD−/− mice compared with age-matched WT littermates. Moreover, JunD may be a crucial modulator of ROS-mediated human vascular aging, representing a novel molecular target for vascular disease prevention.
Recently, perivascular adipose tissue (PVAT) has been shown to play a crucial role in the development of atherosclerosis; however, the effects of AT1 on PVAT properties and their functional relevance in atherogenesis remain undefined.

**Method and Results:**
We examined the fate of specific differences in adipose tissue among epididymal VAT, PVAT surrounding thoracic aorta, and intercapu- lar brown adipose tissue (BAT) in 8-week-old apoe-/- (apoE-/--) mice. The expression of known adipocyte marker genes (UCP-1, PGC-1α, PPARδ, and Cidea) were significantly higher in BAT and VAT compared with WAT (p < 0.01). White adipocyte marker genes (Igf3, Dpt, Tcf21, and Hoxc9), which were hardly expressed in BAT showed a moderate expression in VAT, suggesting that VAT has a strikingly different phenotype from the classical VAT and BAT. We next examined the properties of PVAT in 8-week-old apoe-/-/AT1 receptor deficient (AT1r-/--) mice. After 4 weeks of western diet, the expression levels of adipocyte differentiation marker genes (PPARγ, FABP4, eCBP4) were markedly increased in apoE-/-/ PVAT (p < 0.05), which was completely diminished in apoe-/-/AT1 (p < 0.01). To investigate the effect of AT1 on the perivascular adipocyte differentiation, we performed primary culture of adipocyte from stromal vascular fraction in Agtr1--/- and Agtr1+/+ PVAT. The mRNA expressions of adipocyte differentiation marker genes (PPARγ, FABP4, and eCBP4) were time-dependently increased in Agtr1--/- adipocytes, whereas PPARγ did not differ between the two groups during differentiation. Our findings demonstrate that AT1 regulates the expression levels of late stage of adipocyte-differentiation marker genes in PVAT, suggesting that AT1-mediated modulation of perivascular adipocyte differentiation could be a novel therapeutic target for the prevention of atherosclerosis.

**Methods:**
78 patients with renovascular hypertension, aged 63.8 ± 10.7, who underwent PT A for RAS > 60%. 51% (n = 56) with eGFR > 60mL/min and 25% (n = 22) after hypertension crisis. Clinical data, serum level of NGAL, creatinine (Cr) and BNP, mean systolic and diastolic blood pressure (SBP and DBP), left ventricle mass (LVMI) and diastolic function (E/A, e’ velocity, E/e’ ratio) were analyzed before PT A. The incidences of cardiovascular (CV) death, myocardial infarction (MI), is- chemic stroke (IS) and heart failure (HF) were recorded. The incidences of CV events were determined for 3 years after PT A. The incidences of CV death, MI, and HF were enhanced in patients with NGAL levels above the median in the early and late inflammatory phases after MI. The combined risk of CV death, MI, and HF was enhanced in patients with NGAL levels above the median in the early and late inflammatory phases after MI. The combined risk of CV death, MI, and HF was enhanced in patients with NGAL levels above the median in the early and late inflammatory phases after MI.
was to determine new compositional and structural features of coronary plaques based on automated, objective analysis of VH-IVUS images.

Methods: A biometric computational analysis based on backtracking programing was applied, with emphasis given on the low computational cost and processing time. Single and sequences of VH-IVUS images were analyzed. For each image analysis 29 parameters were computed. Results: The basic plaque characteristics (lumen, vessel areas, percent of stenosis, area and percent of each plaque component), the following parameters related with the spatial distribution and the homogeneity of plaque components were computed: a) the percent of the lumen border that is surrounded by each component, b) the number of different segments and the area of the largest solid segment of each component adjoining to the lumen border, and c) the number of different segments and the area of the largest single segment of each component within the plaque area. A sequence of VH-IVUS images that is recorded during catheter pullback along the coronary vessel is then analyzed in order to automatically classify the examined plaques as thin cap fibroatheromas, the most common type of vulnerable plaque. The classification is made according to standard criteria: a) The percent of the necrotic core area is ≥10%, the necrotic core covers more than 1/3 of the lumen border and c) the two previous conditions are met for at least three serial frames of the images sequence. The total number of sequential and non-sequential frames that meet the criteria (a) and (b) are also determined.

Conclusions: The quantifiable features of plaque components' distribution and heterogeneity provided by the proposed system could provide further insight in the assessment of vulnerable plaques. Especially features of necrotic core and calcification in relation to lumen border may by significant determinants of plaque vulnerability and plaque-sten t interaction. In this respect these new computed data might be useful for the detection of the vulnerable plaque as well as for the evaluation of stent deployment and selection.

Hypoxia reoxygenation-induced endothelial barrier failure: Role of RhoA, Rac1, and MLCK

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Background: Loss of endothelial barrier function leading to oedema formation during hypoxia-reoxygenation presents major impediment for the recovery of the organ. This loss of barrier function is mainly due to loss of cell-cell adhesions and endothelial cell contractile activity. Several signaling pathways including RhoA/Rock and Ca+2/PKC are activated during reoxygenation which could mediate barrier failure, but the precise role of these pathways is still elusive. The aim of the present study was to analyse the role of these signaling pathways in reoxygenation-induced barrier failure.

Methods: In cultured porcine aortic endothelial cells, the effect of hypoxia (30 min, PO2=5 mmHg; pH 6.4) and reoxygenation (45 min, PO2=140 mmHg; pH 7.4) was analyzed on endothelial permeability (albumin flux), contractile activity (MLC phosphorylation), Ca2+, PKC, RhoA, Rac1 (pull down assay), and cell-cell adhesions (confocal microscopy). BAPTA (10 μM), BIM (100 μM), G3Transferase (1 μg/ml), and Y27632 (10 μM) were used to inhibit Ca2+, PKC, RhoA, and Rock signaling, respectively.

Results: Reoxygenation lead to 150±7% increase in permeability, 2.5-fold MLC phosphorylation, and 2.5-fold Rac1 activation but had no effect on RhoA or MLC. Inhibition of MLC kinase (ML-7 10 μM) along with Epac activation had an additive effect. The results were confirmed using isolated perfused rat hearts.

Conclusions: The present data suggest that Rho/Rock and Ca+2/PKC pathways are required for resealing of junctions and inhibition of these pathways can exacerbate the reoxygenation injury. Activation of cAMP/Epac pathway along with inhibition of contractile activation presents a new therapeutic intervention to prevent reoxygenation-induced vascular leakage.

Uric acid levels are associated with asymmetric dimethylarginine, L-arginine and arterial stiffness in hypertensive hypertensive patients


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Purpose: Elevated uric acid (UA) levels are associated with increased cardiovascular risk, while arterial stiffening, L-arginine and asymmetric dimethylarginine (ADMA) contribute to diffuse vascular dysfunction. In this study, we investigated the relationships between UA levels, L-arginine, ADMA and arterial stiffness in essential hypertensives.

Methods: In our population of 180 newly diagnosed untreated non-diabetic patients with hypertension (118 men, age 49 years, office blood pressure (BP)=153/97 mmHg), the distribution of UA was split by the median (5.2 mg/dl) and accordingly subjects were classified into those with high and low values. In all participants, arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior SP).

Results: Patients with high UA (n=91) compared to those with low UA (n=89) exhibited higher 24-h systolic BP (138±8 vs 131±11 mmHg, p<0.0001) while they did not differ regarding metabolic profile (p=NS). Those with high UA compared to those with low UA had increased levels of ADMA (0.5±0.03 vs 0.41±0.05 μmol/l, p<0.0001), L-arginine (102±3.1 vs 78±2.9 μmol/l, p<0.0001) and PWV (8.3±1.6 vs 7.5±0.9 m/sec, p<0.001), independently of confounders. In the entire population, ADMA was correlated with 24-h systolic BP (r=0.265, p=0.05), L-arginine (r=-0.462, p=0.0001) and PWV (r=0.234, p=0.0001). In multiple regression analysis, body mass index (b=0.223, p=0.002), 24-h systolic BP (b=0.196, p=0.004), ADMA (b=0.315, p=0.001) and PWV (b=0.178, p=0.05) were independent predictors of UA.

Conclusions: Increased UA levels in essential hypertension are associated with a state of pronounced endothelial dysfunction and accelerated arterial stiffening. These findings suggest that UA is interrelated with diverse pathological vascular dysfunction, underscoring its mainstay role in the progression of the hypertensive atherosclerotic disease.

The paraoxonase 55 L/M polymorphism influences the onset of acute coronary syndrome but not stable angina

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The paraoxonase1 (PON1) is an antioxidant enzyme synthesized by liver. It has two known polymorphisms: 192 Q/R and 55 L/M. Multiple studies, including our, have associated these polymorphisms with coronary artery disease (CAD) risk. In CAD coexists changes in the vessel wall in emphasis on atherosclerosis, clinically expressed by stable angina (SA), and acute thrombotic changes, expressed by acute coronary syndrome (ACS). However, the mechanism by which these variants influence the CAD susceptibility is still unknown.

Objective: The aim of this study was to evaluate whether PON1 polymorphisms influence the onset of ACS or SA.

Methods: Two case-control studies were performed. The first one included 1665 individuals, 728 with CAD and hospitalized with ACS (mean age 53.3±7.9 years, 73.9% male) and 937 controls without CAD (mean age 52.6±8.0 years, 78.8% male). The second one included a total of 1009 individuals; 208 consecutive patients with SA and significant CAD confirmed by coronary angiography (mean age 56.0±6.8 years, 71.3% male) and 800 controls without CAD (mean age 55.6±5.8 years, 72.9% male). In both studies, cases and controls were matched by gender and age. PON1 variants were analyzed using specific primers. The equilibrium of Hardy-Weinberg was investigated and a bivariate analysis (tables 3x2), with the odds ratio (OR) and 95% confidence interval (CI), was performed in order to determine the CAD risk. A p-value <0.05 was considered statistically significant.

Results: PON 55 MM genotype showed an increased risk for ACS, with an OR of 3.38 (95% CI: 1.38-8.12) but not for SA (OR=1.00, p=0.994). PON 192 Q/R was not significantly associated either with the ACS or with SA.

Conclusions: This study supports the concept that PON 55 MM is an initiator factor of ACS. Not leading to stable angina but to ACS, this polymorphism may be particularly deleterious and may be involved in thrombotogenic and athero- genic mechanism. The patients carrying this genotype should be approached with particular care in terms of primary prevention, possibly through antiplatelet or anticoagulant drugs.

Angiotensin II induces early mechanical heterogeneity along the abdominal aorta, preceding murine aeurysm formation

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Background: Abdominal aortic aneurysm (AAA) pathogenesis involves a broad spectrum of inflammation, cellular proliferation and extracellular matrix alteration. However, little is known about the initiation of aneurysm growth in animal models. Localized chemical damage to the aortic wall is used to trigger a focal vascular demarcation, eventually resulting in AAA. In contrast, suprarenal AAA can readily be induced in apoE−/− mice by systemic Angiotensin II (AngII) infusion without any focal vascular manipulation. This study was designed to test the hypothesis that systemic AngII infusion induces focal mechanical alterations (i.e. heterogeneous strain along the abdominal aorta) that may initiate AAA formation.
Materials and methods: AngII (1000ng/kg/min) or saline (control) was infused via osmotic pump in 10-week-old apoe-/- male mice (C57BL/6J background). At baseline and after 2 days of treatment, systolic (SD) and diastolic (DD) diameters of suprarenal (SR) and infrarenal (IR) aortic segments were measured using M-mode ultrasonography, and strain was calculated as (SD-DD)/DD. Strain ratio along the abdominal aorta was calculated as SR-strain/IR-strain. Gene expression analysis using angiopoietin type 1b receptor (Agtr1b) qRT-PCR was performed to make an mechanistic/vasomotory response to AngII, was measured in SR and IR segments via qRT-PCR.

Results: AngII infusion for 2 days both a significant increase in SR as well as a decrease in IR-strain, resulting in a significant strain heterogeneity (SR/IR strain-ratio: 2.5 ± 0.8 vs. 1.2 ± 0.3 at day 0; p < 0.001). Saline infusion altered none of these parameters. While elevated SR-strain per se failed to demonstrate a correlation to SR diameter changes after 2 days, we found that SR/IR-strain ratio was positively correlated to early SR aortic diameter increase (R²=0.53, p < 0.05). Overt atherosclerosis formation was not detectable after 4 days of AngII infusion, at the earliest. As a possible mechanism for these strain differences, Agtr1b expression was found to be 40-fold higher in IR aorta than in the SR aorta at baseline.

Conclusion: AngII infusion rapidly induces heterogenous strain (SR–IR) along the abdominal aorta, preceding aneurysm formation. These strain differences may be due to initial heterogenous AngII density, and they correlated statistically with an initial dilatation of the aneurysm-prone SR region. These data suggest a mechanism for the early translation from systemic AngII infusion into a focal vascular response (AAA induction), and highlight vascular mechanical heterogeneity as a possible prerequisite of AAA formation.

P4335 Phenotypic characterization of leukocytes at the culprit lesion site in acute coronary syndrome patients

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Background: ST-elevation acute coronary syndrome (STE-ACS) is the leading cause of death in Europe. Mechanisms of coronary plaque rupture are poorly understood.

In contrast to common knowledge implicating monocytes and T-cells in the pathogenesis of acute coronary vascular syndromes, we hypothesize that circulating immunocytes mediate plaque rupture and thrombotic occlusion. The goal of this study was to phenotype inflammatory cells at the site of plaque rupture and to determine their effector functions.

Methods: STE-ACS patients who underwent primary percutaneous coronary intervention at the General Hospital were consented (n=70). Culprit site blood was aspirated with a thrombectomy catheter and particulate thrombus material was separated. In parallel, blood was sampled from the femoral arterial sheath. Flow cytometry was employed to determine cell types accumulating at the plaque rupture site. These results were complemented by ELISA, cell culture and immunofluorescence assays.

Results: The vast majority of inflammatory cells at the culprit lesion site are neutrophils. Coronary neutrophils produce neutrophil extracellular traps, release large amounts of MPO and are apoptosis-resistant. CD4CD200HI T cells are increased with low content of Perkin and Granzyme B. Plate-situte monocyes display a CD14lowCD16high phenotype that is found in aggregation with platelets.

Conclusion: The selective enrichment of innate inflammatory cell subsets at the culprit lesion site suggests a disease-specific inflammatory process, suggesting an outside-in mechanism of acute atherosclerotic vascular obstruction.

P4336 Circulating apoptotic endothelial cells and apoptotic endothelial microcarpichte independently predict the presence of cardiac allograft vasculopathy

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Objectives: Maintenance of endothelial homeostasis may prevent the development of cardiac allograft vasculopathy (CAGV). We investigated whether biomarkers related to endothelial injury and endothelial repair discriminate between CAV positive and CAV negative heart transplant recipients.

Background: CAV is the most important determinant of cardiac allograft survival and a major cause of death after heart transplantation.

Methods: Two patients undergoing coronary angiography between 5 and 15 years after heart transplantation were recruited in this study. Flow cytometry was applied to quantify endothelial progenitor cells (EPCs), circulating endothelial cells (CECs), and endothelial microcarpichte. Cell culture was used for quantification of circulating EPC number and hematopoietic progenitor cell (HPC) number and for analysis of EPC function.

Results: EPC number and EPC function did not differ between CAV negative and CAV positive patients. In univariable models, age, creatinine, steroid dose, granulocyte colony-forming units, apoptotic CECs, and apoptotic endothelial microcarpichte discriminated between CAV positive and CAV negative patients. The logistic regression model containing apoptotic CECs and apoptotic endothelial microcarpichte provided high discrimination between CAV positive and CAV negative patients (C statistic 0.812; 95% CI 0.692-0.932).

In a logistic regression model with age and creatinine as covariates, apoptotic CECs (p=0.0115) and apoptotic endothelial microcarpichte (p=0.0141) were independent predictors (C-statistic 0.855; 95% CI 0.756-0.953). These two biomarkers remained independent predictors when steroid dose was introduced in the model.

Conclusions: The high discriminative ability of apoptotic CECs and apoptotic endothelial microcarpichte is a solid foundation for the development of clinical prediction models of CAV.

P4337 The experimental study of a new kind absorbable magnesium alloy stent

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Background and Objective: At present, the subacute thrombosis and restenosis after stenting can still not be resolved using stainless steel and self-expandable chromium alloy-based drug-eluting stents fundamentally. Thus, the bioabsorbable stent becomes the focus of attention; and now, it is considered that the absorbable magnesium alloy stent is very promising in future. So, we try to study the mechanical compatibility, effectiveness and safety of a new kind stent through animal experiments, which we designed and made by ourself.

Methods: The 35 immunized hybrid dogs were randomly divided into 7 experimental groups, included: control, 24 h, 3, 7, 14, 21, 28 days’ groups, and five dogs in each group. An absorbable magnesium alloy stent was implanted in coronary artery and femoral artery in almost each experiment dog respectively. Each dog was reviewed the coronary and femoral angiography, and then the stent arteries were isolated for histopathological analysis at experimental end. Also, we measured the elastic lamina area, lumen area, and the percentage of intimal hyperplasia area with the computer image analysis software.

Results: 51 Stents were implanted in 35 dog’s coronary and femoral artery successfully. After stenting 24 h,3,7,14,21,28 days, the reviewed coronary and femoral artery angiography showed that stent was completely degraded in 7 days, and the lumen of stenting vessels were patency without remarkable stenosis. Histopathological study showed that there was no intimal hyperplasia of 24 h, 3, 5, 7 days later in stenting vessels; there was only a slight intimal hyperplasia after 2 to 4 weeks, but no significant inflammatory response and thrombosis formation during 4 weeks. The intimal hyperplasia area in each 2, 3, to 4 weeks group was (0.04±0.03)mm², (0.10±0.03)mm², (0.15±0.04)mm², and the percentage of intimal hyperplasia area were 1.84±1.18, 3.72±1.12, 6.29±3.36 respectively, all these increased significantly compared each other (P<0.05).

Conclusions: In the canine model the absorbable magnesium alloy stent, which was absorbed in one week, has good biocompatibility and safety; there was no significant inflammatory response and thrombosis formation, also the intimal hyperplasia and restenosis was very slight after 4 weeks stenting. So, this may be a promising coronary stent in future.

P4338 Angiotensin-(1-7) suppresses the number and function of the circulating fibrocytes by upregulating endothelial nitric oxide synthase expression

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There is growing evidence suggesting that circulating fibrocytes (CFs) play a pivotal role in tissue repair and fibrosis. In contrast, in recent studies, Angiotensin-(1-7) (Ang-(1-7)) has shown to antagonize fibrosis. The purpose of this study is to examine the direct effect of Ang-(1-7) on CFs. Total mononuclear cells (MNCs) were isolated from peripheral blood by Ficoll density gradient centrifugation. U87MG astrocytes seeded in perfusion confocal microfluidics bioreactor confirmed that the stents showed positive for both CD34 and collagen-I. After 14 days of culture, CFs were stimulated with Ang-(1-7) at concentrations of 10nM, 100 nM, 1μM or 10 μM. In the presence and presence of preincubation with A-779 (endothelin receptor type A antagonist) or LNAME (endothelin receptor type B antagonist) or both, for 24, 48 or 72 h. The number of cells, cellular proliferation and level of apoptosis were determined by hematoxylin and eosin staining, the Cell Counting Kit-8 (CCK8) assay and the annexin Vpropidium iodide binding assay, respectively. The collagen content of CFs was measured by the concentration of hydroxyproline, which was detected using the enzymatic digestion method. The expression of endothelial nitric oxide synthase (eNOS) was assayed by western blot analysis, while nitric oxide (NO) generation was detected using the Griess method. We found that Ang-(1-7) increases apoptosis and eNOS/NO production in CFs. In addition, Ang-(1-7) decreases the number, proliferative capacity and collagen-secretion of CFs in a concentration-dependent manner. These data suggest that Ang-(1-7) suppresses both the number and function of CFs possibly by increasing eNOS/NO production in the CFs.
Wnt4 contributes to intimal thickening by promoting VSMC proliferation via up-regulation of RCAN1

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Purpose: We investigated whether Wnt4-induced VSMC proliferation utilizes nuclear transcription factor of activated T-cells (NFAT) as a downstream effector as well as β-catenin. Vascular smooth muscle cell (VSMC) proliferation causes intimal thickening observed in early atherosclerosis and restenosis. We previously demonstrated that Wnt4/β-catenin signalling stimulates VSMC proliferation in vitro via cyclin D1 up-regulation and promotes intimal thickening. Although the “canonical” Wnt/β-catenin pathway plays a vital role in the promotion of Wnt4-driven VSMC proliferation, Wnts can also signal independently of β-catenin, amongst others via a calcium-related pathway involving NFAT. Here we assessed the role of NFATc1 (the predominant isoform in VSMCs) and the induction of known NFAT-responsive genes in Wnt4-induced VSMC proliferation and intimal thickening.

Methods: VSMCs were cultured and in some cases subjected to siRNA; extracted mRNA was analysed by Q-PCR while protein was assessed by Western blotting and/or immunocytochemistry. Mouse carotid arteries were ligated to induce intimal thickening and lesions were analysed by immunohistochemistry.

Results: Additional of recombinant Wnt4 protein in vitro induced a significant increase in the percentage of VSMCs with nuclear NFATc1 within 4h (by 2.4±0.83 fold, p<0.05, n=3), directly demonstrating the activation of Wnt/Ca2+ pathway by Wnt4. Recombinant Wnt4 protein treatment for 6h in vitro significantly up-regulated the mRNA levels of two previously identified NFAT-responsive genes, regulator of calcineurin 1 (RCAN1) and cyclooxygenase 2 (Cox2) as well as Cyclin D1, by 1.54±0.28, 1.39±0.24 and 1.35±0.15 fold respectively (p<0.05, n=3). Treatment with NFAT inhibitor (11R-IWIT) for 24h in vitro significantly retarded Wnt4-induced VSMC proliferation from 46±5% to 30±0%. A protein knockdown (by 89±1%) of NFATc1 in vitro resulted in a significant reduction of both Cyclin D1 and RCAN1 mRNA by 21±7% and 21±7% respectively (p<0.05, n=3). Finally, we observed elevated NFATc1 protein levels while RCAN1 protein was significantly increased in ligated mouse carotid arteries when compared to unligated control arteries (161±16.1 vs 26±7.3 fluorescent pixels per area unit respectively, p=0.05).

Conclusions: Wnt4 is an important contributor to intimal thickening by playing a key role in the stimulation of VSMC proliferation via activation of both “canonical” β-catenin and “non-canonical” NFAT downstream pathways. We show here for the first time that RCAN1, a downstream target of NFAT, is up-regulated by Wnt4}

During reperfusion causes intimal thickening observed in early atherosclerosis and restenosis. The vessel wall especially of the small pulmonary vessels thickens triggered by an abnormal proliferation and migration of vascular smooth muscle cells (VSMCs). The animals were equally divided into 2 groups: BMS vs. SES and BMS vs. CES. Stents were imaged in vivo using OCT at 28 days in 4 animals and after 90 days in the remaining 12 animals. OCT assessment of stent coverage was performed by classifying all visible struts and computing % of well- and malapposed struts, with and without endothelialization. Additionally, an algorithm of quantification of neointimal growth was implemented (Figure) and applied to different stent segments and adjacent vessel areas.

Results: All struts were well apposed without significant differences in endothelialization between BMS, SES and CES. Relative proliferation area (% of lumen), calculated as neointimal area within a stent segment in relation to the stent area was significantly smaller in CES, but not in SES as compared to BMS (Figure).

Conclusions: The novel polymer-free ciprofloxacin-coated stent proved significant anti-restenotic efficacy without delaying endothelialization in this rabbit model and therefore merits attention as a promising stent development.

A non-polymeric ciprofloxacin-eluting stent inhibits neointimal proliferation stronger than sirolimus-eluting stents: an experimental study using optical coherence tomography in rabbit iliacal arteries

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Background: Drug-eluting stents (DES) are currently the best choice to reduce restenosis after coronary stenting. Optical coherence tomography (OCT) is a high-resolution intravascular imaging technique that precisely quantify neointimal proliferation and endothelial strut coverage.

Objective: To investigate ciprofloxacin, a peroxisome proliferator-activated receptor gamma agonist as a novel stent coating.

Methods: Bare metal stents Yukan Choice 2.5/12 mm with microporous surface (BMS) were polymer-free coated with either sirolimus (SES) or ciprofloxacin (CES) at 225 mcg/cm. Sixteen New Zealand White rabbits fed with western diet underwent implantation of different stents in both iliacal arteries via the carotid artery. The animals were equally divided into 2 groups: BMS vs. SES and BMS vs. CES. Stents were imaged in vivo using OCT at 28 days in 4 animals and after 90 days in the remaining 12 animals. OCT assessment of stent coverage was performed by classifying all visible struts and computing % of well- and malapposed struts, with and without endothelialization. Additionally, an algorithm of quantification of neointimal growth was implemented (Figure) and applied to different stent segments and adjacent vessel areas.

Results: All struts were well apposed without significant differences in endothelialization between BMS, SES and CES. Relative proliferation area (% of lumen), calculated as neointimal area within a stent segment in relation to the stent area was significantly smaller in CES, but not in SES as compared to BMS (Figure).

Conclusions: The novel polymer-free ciprofloxacin-coated stent proved significant anti-restenotic efficacy without delaying endothelialization in this rabbit model and therefore merits attention as a promising stent development.

P4341 Functional inhibition of microRNA-92a increases endothelial regeneration and reduce neointimal formation after vascular injury by targeting kruppel-like factor-4

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Purpose: One of the mechanisms responsible of late stent thrombosis after Drug Eluting Stent (DES) implantation is that endothelial recovery is inhibited by the antiproliferative approach, which, although intended to prevent smooth muscle cell proliferation and migration of ECs. Recently, the key breakthroughs for the study of gene expression regulation has been the discovery of microRNAs. MicroRNAs are small non-coding RNAs of 20-22 nucleotides that regulate, at post-transcriptional level, gene expression. Therefore, the aim of the present study was to evaluate the role of microRNA-92a on ECs and VSMCs proliferation and migration in vitro as well as after balloon injury or arterial stenting in vivo.

Methods: ECs and VSMCs proliferation and migration were measured by BrDU incorporation and wound healing assays. In the in vivo protocol, balloon-injury or stenting of the carotid artery were produced in male Wistar rats. Moreover, inhibition of microRNA-92a expression was assessed in vivo by systemic administration of antagonimR-92a. Immunohistochemical staining for von Willebrand factor (vWF) and planimetric analysis after in vivo injections of Evans Blue dye were employed to analyze the process of re-endothelialization. Fixed carotid arteries were stained with hematoxylin/eosin 14 days after balloon-injury to assess neointimal formation.

Results: mir-92a was highly expressed in ECs but to a much lower extent in VSMCs. Importantly, BrD incorporation and wound healing assay provide evidence that functional inhibition of miR-92a resulted in an increased proliferation and migration of ECs but not of VSMCs in vitro. Immunoblotting analysis revealed an increased phosphorylation of eNOS in ECs as a consequence of miR-92a inhibition. Therefore, functional inhibition of miR-92a stimulated nitric oxide (NO) production in ECs. Using reporter lucerase assay, we identified specific targets of miR-92a: KLF4, key regulator of endothelial homeostasis, and MKK4, component of the mitogen-activated protein kinase (MAPK) pathway. Finally, in vivo administration of antagonimR-92a increased re-endothelialization in injured carotid arteries and reduced neointimal formation after balloon-injury or arterial stenting.

Conclusions: These data provide the first evidence that inhibition of miR-92a may represent a novel strategy to improve endothelial regeneration and reduce restenosis after vascular injury. This new approach could be used to design new stents aimed to increase the reendothelialization and eventually to reduce the occurrence of stent thrombosis.

The PI 3-kinase isofrom p110alpha promotes vascular remodelling in pulmonary arterial hypertension

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Purpose: Vascular remodelling is a major characteristic of pulmonary hypertension. The vessel wall especially of the small pulmonary vessels thickens triggered by an abnormal proliferation and migration of vascular smooth muscle cells (VSMCs). In vitro assays demonstrated that the PI3-kinase isofrom p110 alpha is crucial for growth factor induced SMC proliferation and migration. However the role of the PI3-kinase (PI3K) isofrom p110 alpha for vascular remodelling in pulmonary hypertension is poorly understood. We assessed the function of p110 alpha for...
vascular remodelling in the hypoxia induced mouse model of pulmonary hypertension.

Methods: We generated a smooth muscle specific p110 alpha deficient mouse and subjected it to chronic hypoxia to induce pulmonary hypertension. Right ventricle (RV) systolic pressure was determined via invasive measurement using a millar pressure catheter. RV hypertrophy was assessed as ratio RV weight to LV + septum weight. Left ventricular remodelling was quantified and demonstrated as medial wall thickness and degree of vascular muscularization. Results: RV systolic pressure in consequence to hypoxia was decreased in the p110 alpha deficient mice compared to wild-type littermates. Consistently, hypoxia induced RV hypertrophy was significantly reduced in hearts of p110 alpha deficient mice in comparison to wild-type hearts. Medial wall thickness of vessel with a diameter less then 50μm was significantly narrowed in lungs of SM-specific p110 alpha KO mice. Morphometric analysis of the small pulmonary vessels (diameter <70μm) also revealed a smaller fraction of fully and partially muscularized vessels in hypoxia treated p110 alpha deficient mice in comparison to hypoxia treated wild-type mice.

Conclusion: These results indicate that the PI3K isoform p110 alpha is crucial for vascular remodelling in hypoxia induced pulmonary hypertension. A SM-specific loss of p110 alpha prevented vascular remodelling and would therefore represent a promising therapeutic approach.

P4343 Two-chain High Molecular Weight Kininogen (HKa) inhibits neointimal lesion formation by preventing leukocyte recruitment

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Purpose: The cleavage of single-chain high molecular weight kininogen (HK) results in the release of bradykinin and two-chain HK (HKa). HKa and in particular its peptide domain 5 (DS) exert anti-adhesive properties during inflammatory cell recruitment via binding to extracellular matrix proteins and impeding the function of the β2-integrin molecule Mac-1 (CD11b/CD18). In this study, we investigated the effects of HKa and DS on the accumulation of circulating cells and the function of resident vascular cells in a mouse model of neointima formation.

Methods: After lethal irradiation C57BL/6 mice were transplanted with bone marrow from transgenic mice expressing enhanced green fluorescence protein (EGFP). Wire induced injury of the femoral artery was performed on chimeric mice with local application of HKa, DS, or control to the dilated artery in a therapeutic strategy for attenuating atherosclerosis or neointimal lesion development. The process of re-endothelialization were not different. Although the absolute numbers of apoptotic vascular cells as well as the process of trans-differentiation of BM-derived cells into smooth muscle cells/ macrophages in the treatment groups. Confocal microscopy revealed that EGFP+-cells did not co-express smooth muscle myosin heavy chain or calponin, indicating no trans-differentiation of BM-derived cells into smooth muscle cells.

Results: Neointima formation was significantly reduced after treatment with HKa and even more prominent after DS application (HKa: 0.981±0.174; DS: 0.549±0.078 vs. 1.54±0.150, P<0.05). The attenuation of the neointimal lesion was accompanied by a reduced accumulation of EGFP+-cells and monocytes/macrophages in the treatment groups. Results indicated no trans-differentiation of BM-derived cells into smooth muscle cells.

Conclusion: These results indicate that the PI3K isoform p110 alpha is crucial for vascular remodelling in hypoxia induced pulmonary hypertension. A SM-specific loss of p110 alpha prevented vascular remodelling and would therefore represent a promising therapeutic approach.

P4345 Valdsarin inhibits aortic remodeling by blocking transforming growth factor-β1-Smads pathway in diabetic rats

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Objective: Angiotensin II (Ang II) and transforming growth factor β1 (TGF β1) are closely involved in the pathogenesis of diabetic complications. We aimed to determine whether an aberrant thrombospondin 1 (TSP1)–mediated TGF β1-Smads pathway is activated in the pathogenesis of diabetic complications. We aimed to determine whether an aberrant thrombospondin 1 (TSP1)–mediated TGF β1-Smads signaling pathway was activated in diabetic complications. We aimed to determine whether an aberrant thrombospondin 1 (TSP1)–mediated TGF β1-Smads signaling pathway was activated in diabetic complications. We aimed to determine whether an aberrant thrombospondin 1 (TSP1)–mediated TGF β1-Smads signaling pathway was activated in diabetic complications. We aimed to determine whether an aberrant thrombospondin 1 (TSP1)–mediated TGF β1-Smads signaling pathway was activated in diabetic complications.

Methods: Age-matched male Wistar rats (200-240 g) were randomly divided into 3 groups: control (n=4), diabetes (n=16) and valsartan (30 mg/kg/day) (n=16). Type 2 diabetes mellitus (T2DM) was induced by a high-calorie diet and streptozotocin injection. Morphological and biomechanical properties of the thoracic aorta were assessed by echocardiography and carotid catheterization. Masson staining was used for histological evaluation of collagen. The expression of components in the TSP1–mediated TGF β1-Smads signaling pathway was analyzed by immunohistochemistry and real-time quantitative RT-PCR.

Results: Compared with control mice, diabetic aortas showed reduced distensibility and compliance, with excess collagen deposition. Components in the TSP1–mediated TGF β1-Smads signaling pathway was analyzed by immunohistochemistry and real-time quantitative RT-PCR.

Conclusions: Valsartan inhibits aortic remodeling by blocking transforming growth factor-beta-1-Smads pathway in diabetic rats.

P4344 Hyaluronidase activity is increased in human abdominal aortic aneurysm

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Background: Hyaluronidase (HA) is expressed in atherosclerotic lesions, but its exact role in abdominal aortic aneurysm remains unknown. As degradation of hyaluronic acid by hyaluronidase into low molecular weight hyaluronic acid (LMW-HA) is associated with inflammation and matrix metalloproteinase (MMP)-9 activity, we hypothesized that hyaluronidase activity is increased in abdominal aortic aneurysm, especially the area between almost normal margin and maximum diameter. Those area were characterized by high number of macrophage, MMP-9 activity, and destruction of elastin.

Methods: Five specimens were obtained as a whole abdominal aortic tissue (from proximal margin to distal margin). A whole sample was categorized into three zones; zones of (1) margin, (2) middle, and (3) maximum diameter (Figure A). Then, whole tissue were cut into around one inch of pieces, and characterized for the histological parameters: macrophage, expression of CD44, and destruction of elastin. The activity of hyaluronidase, expression of CD44, and activity of hyaluronidase were determined by ELISA.

Results: Hyaluronidase activity, LMW-HA and CD44 expression levels were increased in middle zone compared with zones of margin and maximum diameter (Figure B and C). MMP-9 activity correlated with the expression of CD44, hyaluronidase activity and LMW-HA concentration. In vitro stimulation of macrophages with LMW-HA increased MMP-9 activity and inflammatory cytokines.

Conclusions: These results indicate that the PI3K isoform p110 alpha is crucial for vascular remodelling in hypoxia induced pulmonary hypertension. A SM-specific loss of p110 alpha prevented vascular remodelling and would therefore represent a promising therapeutic approach.
A novel adipocytokine, CTRP9 attenuates vascular smooth muscle cell proliferation and neointimal formation after vascular injury

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Background: C1q/TNF-related protein (CTRP) 9 is a novel adipokine that has beneficial effects on glucose metabolism and endothelial function. However, the role of CTRP9 in vascular remodeling is unknown. Here, we investigated the effect of CTRP9 on vascular smooth muscle cell (VSMC) proliferation and neointimal hyperplasia in a restenosis model.

Methods and Results: An adenovirus expressing CTRP9 (Ad-CTRP9) or β-galactosidase as a control was injected into the jugular vein of wild-type (WT) mice 3 d prior to vascular injury. Left femoral arteries of mice were injured by a 0.015 inch stainless-steel wire inserted from the lumen. Administration of Ad-CTRP9 increased plasma CTRP levels by a factor of 5.1 ± 0.9 at day 5 after injection compared with control. At 21 days after vascular injury, delivery of Ad-CTRP9 significantly attenuated intimal hyperplasia compared with that of control (p < 0.01, n = 8). Ad-CTRP9 also decreased the number of bromodeoxyuridine (BrdU)-positive proliferating cells in the neointima at day 7 after vascular injury versus control. In cultured VSMCs, recombinant CTRP9 protein attenuated DNA synthesis in a dose-dependent manner. Furthermore, the addition of recombinant CTRP9 significantly inhibited PDGF-β and TGF-β1 synergistic enhancement of ERK phosphorylation.

Conclusion: CTRP9 reduces VSMC growth and prevents neointimal thickening after vascular injury in vivo, suggesting that the therapeutic approaches to enhance CTRP9 production can be beneficial for prevention of vascular restenosis after intervention.

Furin-dependent maturation of proNGF induces migration of vascular smooth muscle cells by TrkA-mediated recruitment of paxillin to focal adhesion sites

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Background: Vascular smooth muscle cell (VSMC) migration is a key feature of vascular restenosis. Recently, it was shown that the nerve growth factor (NGF) and its high-affinity receptor, the neurotrophic tyrosine kinase receptor type 1 (TrkA), are expressed in restenotic lesions. However, the underlying mechanism and functional relevance is poorly understood. NGF is synthesized as a precursor (proNGF) that is cleaved into mature β-NGF by the proprotein convertase furin (PCF) or transforming growth factor-β (TGF-β). The furin inhibitor dec-CMK inhibited furin enzymatic activity and proNGF cleavage, thus abrogating NGF secretion. Migration checker box experiments demonstrated that conditioned medium (CM) of VSMCs stimulated with PDGF-BB/TGF-β1 and recombinant β-NGF induce chemotaxis of rat VSMCs. Immunofluorescence confirmed F-actin rearrangement and recruitment of the integrin adaptor protein paxillin to focal adhesion sites in β-NGF-treated VSMCs. This was accompanied by phosphorylation of Akt and paxillin, which was prevented by both the TrkA-receptor antagonist K252a and the PI3K-inhibitor LY294002. Accordingly, K252a and LY294002 reduced β-NGF-induced migration. Blockade of integrin-mediated outside-in signaling by using RGD-peptides did not affect phosphorylation of Akt or paxillin. Next, we demonstrated that VSMCs can be stimulated to secrete β-NGF when treated with the proNGF-β-NGF in the precursor form of miR-146a that lead to an attenuated migration, sprout formation and vessel network formation. On the other hand, using 2′-O methylated RNA the precursor form of miR-146a targeting miR-146A was significantly downregulated and hence represent molecular targets for miR-146a. Further in vitro analysis showed that miR-146A induction seems to be mediated by NF-κB. In complementing in vivo experiments, inhibition of miR-146A following dilation of the femoral artery was performed. The data of Evans’s Blue and VWF staining showed significantly enhanced restenosis during the in vivo experiments on the C57BL/6/N. The value of DNA synthesis after 21 days of injury was significantly reduced compared with control. Ad-CTRP9 also decreased the number of bromodeoxyuridine (BrdU) positive proliferating cells in the neointima at day 7 after vascular injury versus control. In cultured VSMCs, recombinant CTRP9 protein attenuated DNA synthesis after intervention.

Conclusion: Determining the expression profile of differentially regulated miRNAs in restenosis development, we identified miR-146a likely involved in the disease development and progression and could further increase our understanding of its role in vascular migrations.

MicroRNA-146a and its role in vascular smooth muscle cells during vascular remodeling processes

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Background: MicroRNAs (miRNAs) are a new class of small noncoding RNA molecules, comprising key regulators for major cellular events including proliferation, differentiation and apoptosis. Emerging data suggest that miRNAs that influence the function of the cells of the vascular vasculature like monocytes/macrophages, smooth muscle cells and endothelial cells showed a strong expression of miR-146a, especially in endothelial cells. In vitro, the upregulation of mir-146a could be attributed to the inflammatory stimulus IL-1β. To further assess the functional role of miR-146a in murine smooth muscle cells, we tested the effect of the precursor form of mir-146a on VSMCs. Using real-time PCR tests were performed after overexpression of mir-146a. The transcripts for TRAF6 and IRAK1, two key adapter molecules in TLR- and IL-1 receptor signaling cascades, were significantly downregulated and hence represent molecular targets for miR-146a. Furthermore, using 2′-O methylated RNA the precursor form of miR-146a that lead to an attenuated migration, sprout formation and vessel network formation. On the other hand, using 2′-O methylated RNA the precursor form of miR-146a targeting miR-146A was significantly downregulated and hence represent molecular targets for miR-146a. Thus, these observations add substantially to our understanding of the impact of miRNAs on vascular proliferative diseases.
Ablation of PDGF receptor signaling reduces neointima formation after balloon angioplasty and does not affect the proliferation and migration of endothelial cells

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Despite the introduction of new techniques such as drug-eluting stents, restenosis and stent thrombosis following angioplasty remain serious clinical problems. To prevent neointima formation and the development of stent thrombosis after balloon angioplasty and stent implantation, it is essential to reduce the accumulation of vascular smooth muscle cells (SMC) on the one hand and to ensure the re-endothelialization as far as possible on the other hand. The proliferation and migration of SMCs and endothelial cells (ECs) are mainly induced by receptor tyrosine kinases which are activated by growth factors. Previously, we could demonstrate that the mutation of central binding domains of the platelet-derived growth factor receptor (PDGFR) in a mouse model causes a significant reduction of neointima formation after balloon angioplasty. The influence of an inhibition of PDGFR on endothelial cells is not known.

In this study, we analysed the effects of two PDGF inhibitors (Imatinib and Nilotinib) on proliferation and migration of human endothelial cells (hcECs) and human coronary ECs (hcECs). For this purpose, the cells were stimulated with PDGF (30 ng/ml) or VEGF (50 ng/ml) and various concentrations of imatinib or nilotinib were tested. The cell proliferation was determined by BrdU incorporation assay and chemotaxis using a modified Boyden chamber. Protein expression and activation were investigated by Western blot analyses. Stimulation of hcECs with PDGF induced a 2.9±0.3 fold increase (p<0.05) in proliferation and a 2.6±0.2 fold increase in chemotactic activity (n=3, p=0.005), whereas PDGF had no effect on the proliferation and chemotaxis of hcECs. VEGF induced proliferation (1.9±0.2) and chemotaxis (3.3±0.3) of hcECs. Western blot analyses demonstrated that the expression and activation of PDGFR are limited to hcSMCs while VEGFR expression and activation were restricted to hcSMCs. PDGF-induced proliferation and migration of SMCs were completely inhibited by Imatinib while VEGF-induced proliferation and migration of SMCs was only partially inhibited by Imatinib.

Results:

Imatinib had no effect on VEGF-induced proliferation and migration of SMCs (no inhibition at 10 μM) while nilotinib caused a 50% inhibition of both cell responses at high concentrations (100 μM). Our results indicate that inhibition of PDGFR, especially by imatinib, inhibits the proliferation and migration of SMCs without suppressing the cellular expressions of SMCs. Thus, the PDGFR represents a promising therapeutic target in order to prevent restenosis following percutaneous coronary intervention.

Changes of elastic properties of large arteries in systemic sclerosis are related to endothelial activation and matrix tissue remodelling

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Introduction: Systemic sclerosis (SSc) is a connective tissue disease with characteristic fibrosis of internal organs and abnormalities of small arteries. Pulse wave velocity (PWV) is a simple and non invasive method of evaluation of elastic properties of large arteries.

Aim of the study: The aim of this study was to evaluate the changes in the blood vessels wall in SSc patients and its relation with the biochemical markers of endothelial activation (endothelin-1, ADMA) and marker of matrix remodelling (TIMP-1).

Materials and methods: We prospectively examined 69 consecutive SSc pa-

Results: PWV tended to be higher in SSc than in V. Interestingly in SSc patients PWV correlated with the TIMP-1 serum level (r=0.3; p<0.04) and ET-1 serum level (r=0.3; p<0.009). The ET-1 serum level also significantly positively correlated with TIMP-1 serum level (r=0.4; p=0.002).

Conclusions: SSc patients found to have higher ADMA and ET-1 serum level. ET-1 and TIMP-1 positive correlation and negative correlations between ET-1 and TIMP-1 with PWV suggest that both endothelial dysfunction and matrix remodelling are associated in the pathogenesis of large arteries in systemic sclerosis.

Border zone coronary collateral network detected with an imaging cryomicrotome in the infarcted human heart

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Purpose: To establish the nature of the collateral network connecting tissue adjacent to infarcted tissue.

Methods: A severely hypertrophic human heart of approximately 550 gram became available after abodction. The medical history showed signs of coronary artery disease, high blood pressure and a previous infarct in the posterior free wall. The coronary arteries of the heart were cannulated and flushed with buffer until the efflux remained clear of blood. Vascular casting replica material containing blue fluorescent dye was infused at 100 mmHg and allowed to polymerize. The entire heart was analyzed in a novel imaging cryomicrotome resulting in a full digital 3D reconstruction with a voxel dimension of 32 micrometer.

Results: A maximal intensity projection of a selected area from a slab of tissue 6 mm thick is depicted in the figure. It includes part of the septum and contiguous posterior wall. Left shows all vessels with diameter > 50 micrometer, right only the collateral connections as indicated by the arrow. Few vessels were found in the infarcted area of left ventricular posterior wall. At the imaging settings chosen, quantitative vascular tree analysis yielded 140 collaterals which connected from the LAD transectally towards the LCX while only 4 collaterals were found to connect RA to LCX territory. Septal collaterals were between 50-100 micrometer in diameter but 1-2 cm long and without side branches (see Figure 1).

Conclusions: The collaterals aid in perfusion of the border zone adjacent to the infarcted area. The collateral blood supply is provided by multiple parallel, relatively narrow collateral connections rather than a single conduit like type collateral artery.

Angiotensin II (AngII)-induced arterial remodeling is associated with upregulation of miR-21 and downregulation of miR-29b

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Background: Arterial stiffening is associated with numerous diseases such as hypertension, congestive heart failure, diabetes mellitus and renal failure, and is an independent risk factor for cardiovascular disease. Consequently there is a growing interest in the mechanisms that govern the process of arterial remodeling. Recently, microRNAs (miRs) have emerged as powerful cellular regulators involved in disease and tissue remodeling. More specifically, miR-29b downregulation as well as miR-21 upregulation have been identified as pro-fibrotic mechanisms in various cardiovascular disease models. This study investigated the role of miR-21 and miR-29b in a mouse model of AngII-induced arterial remodeling.

Materials and methods: AngII (1000ng/kg/min) was infused into conscious male C57BL6 mice for 7 days. Subsequently, infrarenal abdominal aortas were harvested and expression of various collagen isoforms known to be crucial determinants of arterial remodeling/stiffening was quantified via qRT-PCR. We then measured expression levels of miR-21 and miR-29b.

Results: AngII stimulation resulted in a marked pro-fibrotic response as evidenced by significant increases in Col1α1 and Col3α1 expression (~3 fold) in the infrarenal aorta compared to baseline levels (p<0.05). This increase was ac-

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SSc (n=69)</th>
<th>Controls (n=21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWV (m/s)</td>
<td>9.7±1.9±2</td>
<td>8.7±2.0±1</td>
<td>0.29</td>
</tr>
<tr>
<td>Endothelin-1 (pg/ml)</td>
<td>1.8±1.3</td>
<td>1.2±0.6</td>
<td>0.006</td>
</tr>
<tr>
<td>TIMP-1 (ng/ml)</td>
<td>204.6±35.0</td>
<td>182.8±28.9</td>
<td>0.12</td>
</tr>
<tr>
<td>ADMA (μmol/l)</td>
<td>0.59±0.34</td>
<td>0.46±0.08</td>
<td>0.01</td>
</tr>
</tbody>
</table>

PWV, pulse wave velocity; TIMP-1, tissue inhibitor of matrix metalloproteinase; ADMA, asymmetric dimethylarginine.
compared by significant downregulation of miR-29b, and upregulation of miR-21 (Figure 1).

Conclusion: The pro-fibrotic response in AngII-mediated arterial remodelling is associated with an increase in miR-21 and a decrease in miR-29b. Modulation of miR-21 and miR-29b have both been successful in altering fibrotic mechanisms in various cardiovascular diseases. These data suggest they may also be potential targets in the treatment of hypertensive vascular remodelling/arterial stiffening.

P4354 Changes of vascular walls in different levels of arterial system in patients with stable coronary artery disease and type 2 diabetes mellitus

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Aim: To assess the relationship between large arterial wall remodelling and changes of microcirculation in small resistance arteries and capillaries in patients with stable coronary artery disease (CAD).

Patient and methods: In patients with CAD (n=25; male: 10; mean age: 62.7±6; BMI: 30.7±4.4) and 25 healthy participants (male: 11; mean age: 57.3±7.9; BMI: 26.3±4.1) digit photoplethysmography and nail fold videocapillaroscopy at resting baseline, during venous occlusion were performed. We evaluated a remodelling of large artery arterial stiffness (SI), augmentation index (AIx75)) and structural changes of microcirculation in small resistance arteries (reflection index (RI)) and capillaries (maximal capillary densities (CD max), coefficient of capillary remodelling (Kdv/ad) diameter of venous part of capillary/diameter of arterial part of capillary).

Results: Measure of remodelling of large vessels Aix75 was significantly higher in CAD patients than in healthy controls (20.4±1.9 vs. 12.3±1.11; p<0.05). There was no different S1 and RI in groups (SI CAD: 7.14±m ≤1.7 vs.7.25±1.88 m/s; p>0.7) (RI Control: 42.4±19.1% vs.51.7±34.5%; p>0.3), while RI was above normal in both groups (norm= 30%).

CD max in CAD group was significantly lower than in control (49,7±6.9cap/mm² vs. 58.6±12.9 cap/mm²; p<0.005). There was no significant difference of Kdv/ad between two groups (CAD vs. Control: 1.13±0.18 vs 1.09±0.25; p=0.6). Aix75 was significantly correlated with RI (rs =0.43; p<0.05). No correlation between Aix75 with CD max (rs = -0.17; p>0.05). RI with CD max (rs = -0.07; p>0.05) was observed.

Conclusions: In CAD patients presents both remodelling of large vessels and structural changes of microcirculation in small resistance arteries and capillaries. Structural changes of small resistance artery may be associated with large artery remodelling, while capillary changes do not. High level of measure of small resistance arterial changes in control group may be associated with the traditional risk factor of cardiovascular in the group.

ASSESSMENT & INTERVENTION TO IMPROVE

P4355 Relationship between red cell distribution width (RDW) and clinical outcomes in non-ST elevation myocardial infarction and unstable angina pectoris: 3-years follow-up

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Purpose: Epicardial adipose tissue represents visceral adiposity and early detection of visceral adiposity could be helpful for assessing subclinical target organ damage. Although previous studies have reported the relationship between epicardial fat thickness and arterial stiffness, there is no report regarding the relationship between EFT and arterial stiffness. The present study was performed to evaluate the association between epicardial fat thickness and arterial stiffness.

Methods: We consecutively enrolled 655 subjects (445 men, 55±9 years), who underwent echocardiography and brachial-ankle pulse wave velocity (baPWV) with ankle-brachial index greater than 0.95. Echocardiographic EFT was measured from parasternal long-axis and short-axis views on the free wall of the right ventricle at the end of diastole. The subjects were divided into four quartile groups depending on EFT (≥3.45 mm, 3.41-3.90 mm, 3.91-4.95 mm, and ≥4.96 mm). Quarts were classified into two groups according to baPWV: group I (324 subjects), baPWV >1366cm/sec; and group II (331 subjects), baPWV ≤1366cm/sec.

Results: The EFT in group II were significantly higher than those in group I (4.2mm versus 3.7 mm, p<0.001). There were significant differences in baPWV value among the four quartile groups of the EFT (quartile I, 1.327±148.8 mm/sec; quartile II, 1.371±215.0 cm/sec; quartile III, 1.434±228.3 cm/sec; quartile IV, 1.507±233.1 cm/sec; p-value ≤0.001). In the multivariate linear regression model adjusted for age, sex, lifestyle status, systolic blood pressure, heart rate, fasting glucose, triglyceride, high-density cholesterol, homeostasis model assessment-insulin resistance, and high-sensitivity C reactive protein, the absolute values of EFT were an independent determinant of increasing baPWVs in the above model [standard β=0.113, p=0.001]. In the same model for logistic regression analysis, increasing quartiles of EFT showed a significant association with increased baPWV group (p for trend=0.010) and the highest quartile group of EFT had higher odds ratio (OR) for increased baPWV group compared with that of the lowest quartile group (OR [95% confidence interval (CI)]: 2.19 [1.21-3.95]).

Conclusion: This study indicates an independent relationship between epicardial fat thickness and arterial stiffness, suggesting that echocardiographic EFT measurement could be an easy-to-measure and useful tool for early detection of subclinical target organ damage.

P4356 Echocardiographic epicardial fat thickness is associated with arterial stiffness

B.J. Kim, B.S. Kim, J.H. Kang. Division of Cardiology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of Korea

Purpose: Epicardial adipose tissue represents visceral adiposity and early detection of visceral adiposity could be helpful for assessing subclinical target organ damage. Although previous studies have reported the relationship between epicardial fat thickness and arterial stiffness, there is no report regarding the relationship between EFT and arterial stiffness. The present study was performed to evaluate the association between epicardial fat thickness and arterial stiffness.

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Conclusion: This study indicates an independent relationship between epicardial fat thickness and arterial stiffness, suggesting that echocardiographic EFT measurement could be an easy-to-measure and useful tool for early detection of subclinical target organ damage.
Causality of inflammation related to blood leucocyte count for the progression of arterial stiffness and pressure wave reflection

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Background: It has not yet been fully clarified whether elevated serum C-reactive protein levels (cCRP) and peripheral blood leucocyte counts (BLC) are merely markers of arterial stiffening and pressure wave reflection abnormalities, which result from different mechanisms of cardiovascular risk, or whether any causal relationship might exist between these parameters and the aforementioned cardiovascular risk factors.

Objectives: The present 3-year prospective study was conducted to examine this issue.

Methods: Measurements of cCRP, BLC, brachial-ankle pulse wave velocity (baPWV) and radial augmentation index (RAI) were conducted at the baseline and at the end of the 3-year study period in 1291 healthy Japanese men (43±8 years old).

Results: BLC, but not log-transformed cCRP, showed a significant relationship with the baPWV, but not RAI, at both the baseline and the final examinations. Elevated BLC was defined as any count in the highest tertile (BLC > 6400 cells/mm³), and sustained elevation of the BLC was defined as elevated values at both the baseline and the final examinations. The delta change of baPWV (adjusted value) during the study period, but not that of the RAI, was significantly larger in the group showing sustained elevation of the BLC ([54±3.7] cm/sec) than in the group not showing elevation of the BLC in either the baseline or the final examination (32±1.6±3.6 cm/sec) (p<0.05). Similar findings were not observed for sustained elevation of the cCRP.

Conclusion: The facet of inflammation related to elevated BLC, but not that related to elevated cCRP, may be causally associated with the progression of arterial stiffening of the large-to-middle-sized arteries. However, no such association with inflammation was found for progression of abnormalities of the pressure wave reflection.
increased risk of UGIB with alcohol consumption among patients taking low-dose ASA. Three studies found that proton pump inhibitor (PPI) use was associated with a significant reduction in the risk of UGIB in users of low-dose ASA (OR: 0.92 [95% CI: 0.87–0.98]; OR: 0.94 [95% CI: 0.90–0.99]; OR: 0.86 [95% CI: 0.82–0.90]).

**Conclusions:** The risk of UGIB is increased in users of low-dose ASA who have a history of peptic ulcer disease, Helicobacter pylori infection or dyspepsia, cardiovascular disease, diabetes mellitus (DM), and Revised Cardiac Risk Index (RCRI) score ≥3. In patients without DM, RCRI ≥3, high BMI, and current smoking the risk of UGIB is increased by 30.8% vs 9.4%; p < 0.001) and a preoperative serum creatinine higher than 1.4 mg/dL or a history of peptic ulcer disease, Helicobacter pylori infection or dyspepsia; compared with those who never developed AKI.

**Conclusions:** Several preoperative predictors are found to be associated with AKI after noncardiac, nonvascular surgery. Perioperative AKI is an independent risk factor for cardiovascular complications, major bleeding, stroke and in-hospital mortality.

### Table 1. CIN-contrast-induced nephropathy: (+) positive, (–) negative

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CIN (+), n=13</th>
<th>CIN (-), n=31</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSP27 (pg/ml)</td>
<td>2.51 (2.42 – 18.56)</td>
<td>3.89 (1.14 – 23.68)</td>
<td>0.06</td>
</tr>
<tr>
<td>HSP60 (pg/ml)</td>
<td>4.07 (1.07 – 3.07)</td>
<td>0.65 (1.07 – 13.37)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Conclusions:** HSP27 appears to play protective roles in the process of CIN. Serum HSP60 concentration seems to be a marker of increased risk of CIN development induced by PCI.

### Table 2. CIN contrast-induced nephropathy: (+) positive, (–) negative

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CIN (+), n=13</th>
<th>CIN (-), n=31</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSP27 (pg/ml)</td>
<td>0.47 (1.07 – 3.07)</td>
<td>0.65 (1.07 – 13.37)</td>
<td>0.005</td>
</tr>
<tr>
<td>HSP60 (pg/ml)</td>
<td>4.07 (1.07 – 3.07)</td>
<td>0.65 (1.07 – 13.37)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

**Results:** Of 94 patients 13 patients (29.5%) developed CIN. Either HSP27 or HSP60 levels were decreased in patients with treated and controlled diabetes (median: 3.06 ng/ml [1.14 – 23.68] vs 10.77 ng/ml [0.32 – 32]; p = 0.009) and (p = 0.001 respectively). PCI induced the increase (h) of HSP27 but not HSP60 level. Similarly, HSP27 was, however, significantly increased in CIN+ group compared with patients in CIN– group (p = 0.006). In CIN+ group baseline HSP60 level was higher compared with CIN– group (p = 0.001) (Table 1). Baseline HSP60 level correlated positively with Δ creatinine level (r = 0.545, p < 0.001). Similarly, HSP27 correlated with Δ creatinine induced by the PCI procedure (r = 0.473, p < 0.001). Multiple regression analysis indicated high baseline HSP60 serum concentration as independent risk factor for the development of CIN in patients undergoing PCI.

**Methods:** We prospectively included 712 patients. AI was measured by radial artery tonometry and normalized for age, sex and heart rate (75 bpm). AI values were divided into 4 groups according to the following: group 1: < 95th percentile, group 2: between 95th and 99th percentile, group 3: between 99th and 99.9th percentile, and group 4: < 99.9th percentile. AI values were assessed by ultrasound. Four risk groups were made according to the sum of RF (current smoking, hypertension, diabetes and dyslipidemia) and 3 groups (≤ 10%, between 10 and 20% and >20%) according to the 10 year percentage calculated by Framingham.

**Results:** Men represented 56% of the population and mean age was 57 years old. Thirteen percent were treated for diabetes, 48% for dyslipidemia and 49% for hypertension (of which 83% were controlled). Cardiovascular RF groups represented 8%, 42%, 37% and 13% of the population respectively. Patients with chronic disease, diabetes mellitus (DM), and Revised Cardiac Risk Index (RCRI) score ≥3 had significantly more elevated AI values (p < 0.001). AI values distribution was the same in patients with treated and controlled hypertension than untreated normotensives. AI was associated with the presence of renal and carotid plaques (p = 0.001) but not with BMI elevation. Patients with the higher cardiovascular risk scores had AI values lower than 10 years risk higher than 10% and significantly increased AI values (p < 0.0001) without any relationships found between AI and pulse pressure, diabetes, HbA1C, or dyslipidemia parameters.

**Conclusions:** An elevated AI measured at radial artery and adjusted for sex, age and heart rate reflects elevated BP and is strongly associated to 10 years cardiovascular and atherosclerotic lesions. This study suggests that AI could be an integrator of vascular damages.

**Methods:** We retrospectively enrolled 651 consecutive South Korean individuals who had been admitted to our institute and had undergone baPWV and ECG for suspected coronary artery disease between June 2010 and July 2011. AI value was calculated by a multivariable logistic regression analysis with cardiovascular disease as the primary outcome. The associations between arterial stiffness, as determined by baPWV and the extent of coronary artery disease, as detected by coronary angiography (CAG).

**Results:** By multivariable logistic regression analysis, significant predictors of coronary artery disease (CAD, diameter of stenosis ≥50%) were male gender, age, high density lipoprotein cholesterol, HbA1C and the level of baPWV. When we divided subjects into 3 groups according to clinical outcomes, the value of baPWV.
The existence of non-obstructive plaque in carotid artery predicts cardiovascular death in patients of end-stage renal disease on maintenance hemodialysis

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Purpose: Patients of end-stage renal disease (ESRD) are well known to suffer from higher mortality than normal population. It is said, the longer the renal re-placement therapy, the more advanced the atherosclerosis, which has been contributing prominently to the high cardiovascular mortality. Carotid intimal thickness (CIMT) offers an easy access to explore the status of systemic atherosclerosis. In this study, we follow the cohort to figure out the significance of CIMT and other factors, which may impact the clinical outcome of ESRD patients.

Methods: This is a cohort study conducted in a tertiary referring medical center. All enrollee should be patients of ESRD, who has received maintenance hemodialysis (HD) for more than 3 months. In Feb. 2007, one cardiologist finished the carotid duplex within one week, during which all enrollee received blood sampling for various lab tests. All the patients were closely followed with clinical events recorded. The primary endpoint was cardiovascular death. In statistics, significance is defined by p < 0.05.

Results: There were 265 patients in this cohort, and the distribution of gender was nearly equal (male vs female: 49.1% vs 50.9%). The age of this cohort is 61.2 ± 12.4 year-old and these patients have been put on HD for 42.7 ± 39.3 months. After 2-year follow, 11.7% of the patients expired for cardiovascular causes. Those who reached the primary endpoint were older (68.2 ± 13.3 vs. 60.3 ± 12.3 year-old), with higher fasting blood sugar (161.1 ± 87.0 vs 117.5 ± 66.1 mg/dl), lower sodium (141.2 ± 4.0 vs 144.2 ± 3.3 mEq/dl), higher C-reactive protein (CRP) (2.2 ± 4.7 vs 0.8 ± 1.5 mg/L), thicker CIMT over left carotid artery (0.56 ± 0.017 vs. 0.50 ± 0.015 cm) and more carotid plaque (51.6 ± 24.0%). Those plaques cast 30.5% narrowing over the involved arteries, never resulting in significant stenosis. After logistic regression, the existence of carotid plaque (OR 3.371, 95% CI 1.568-7.251, p = 0.001) correlated with the primary outcome most significantly.

Conclusion: In this 2-year cohort, we discovered that the existence of non-obstructive carotid artery plaques could significantly impose high cardiovascular mortality to ESRD patients on maintenance HD. Further intervention to reduce carotid plaque may improve the primary outcome in this patient population.

Fasting serum apolipoprotein B-48 levels were correlated with the prevalence of coronary artery disease

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Purpose: Many clinical studies have shown that fasting hypertriglyceridemia is one of the independent risk factors for coronary artery disease (CAD) and related to the existence of postprandial hyperlipidemia (PH). In patients with PH, TG-rich lipoproteins and their hydrolyzed product, remnant lipoproteins were accumulated, which were mainly apolipoprotein (apo) B-48-containing lipoproteins, such as chylomicrons and chylomicron remnants (CM-R) derived from the intestine. CM-R had highly atherogenic properties in vitro and possibly developed atherosclerotic plaques, we investigated whether the accumulation of CM-R was correlated with the development of CAD by measuring fasting apoB-48 levels.

Methods: Subjects who received coronary angiography (CAD) and did not take any lipid-lowering drugs (n=189) were enrolled. Those who had angiographically significant coronary stenosis (75% or more luminal diameter stenosis) in left anterior descending artery, left circumflex artery and/or right coronary artery were treated as the patients with CAD (n=96) and age, sex and BMI-matched subjects who did not have significant stenosis were treated as non-CAD subjects (n=83). Both non-diabetics with a history of coronary heart disease (CHD) and diabetics without a history of CHD were further divided into those with and without a history of CHD.

Results: Fasting serum apo B-48 levels were significantly higher in the patients with CAD than in the non-CAD subjects (3.9 ± 2.4 vs 6.9 ± 2.4 mg/dl, p < 0.0001). Multiple regression analysis identified that only apoB-48 was a significant determinant of the existence of CAD (p < 0.0001), among other metabolic parameters related to coronary risk. In patients with high TG, low HDL-C, high HbA1c and low adiponcin levels, the prevalence of CAD significantly increased when their apoB-48 levels were high compared with their apoB-48 levels were low. The clustering of high fasting apo B-48 level and other coronary risk factors was associated with a stronger risk for CAD compared with the single existence of them.

Conclusion: High fasting serum apo B-48 level correlates the prevalence of CAD. The prevalence of CAD significantly was higher in patients with high apoB-48 levels when their metabolic parameters of the metabolic syndrome were impaired.
Development and psychometric properties of the Heart Failure Knowledge Scale in Japan

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Purpose: Heart failure (HF) knowledge is considered to be a cornerstone for HF management. However, there are no valid and reliable instruments available, with acceptable HF knowledge in Japanese. The main purpose of this study was to develop a reliable and valid instrument for the measurement of HF knowledge, and to assess the relationship between HF knowledge and HF self-care behavior.

Methods: We developed a questionnaire consisting of 17 items concerning HF knowledge in reference to the previous studies, such as “HF is a condition that the heart is not able to pump sufficient amount of blood through the body”, “Diuretics remove fluids from the body”, and “HF patients had better drink more water than healthy people”. Patients responded these questions with “yes”, “no”, or “I do not know”. A correct answer was scored 1, an incorrect answer or an answer of “I do not know” was scored 0. Scores for each item were summed, giving a range of total scores from 0 to 17. A higher score indicates greater knowledge about HF. Content validity was confirmed by the expert panel including a cardiovascular nurse and a cardiologist.

Conclusions: Cronbach’s alpha was measured at 0.88, showing adequate reliability. The low HF knowledge score was significantly associated with poor HF self-care behavior, as assessed by the European Heart Failure Self-Care Behavior Scale-Japanese version (r=0.256, p<0.01).

Short duration holter monitoring is equally as good as daily monitoring in heart rate and pause assessment

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Holter monitoring is integral to managing chronic cardiovascular disorders such as heart failure. Accurate heart rate monitoring helps guide nurses and doctors in titrating beta blocker therapy and identification of rhythm disturbances. This is usually achieved by performing 24 hour holter monitoring to assess key variables such as daily heart rate and occurrence of arrhythmias and pauses. The difficulty with this approach is the amount of monitoring that is required, the limited availability of holter monitors and time spent on analysis. These factors impact time and finances in a busy cardiological setting.

We therefore investigated the usefulness of 2, 3 or 4 hour holter monitoring in yielding similar data to the longer 16 hour daily monitoring. We analysed the holter tapes of 50 subjects attending for various cardiological problems. The same tape was used for each analysis and the hours selected for the 2.3 or 4 hour analysis were performed randomly during the normal 9 to 5 pm working period. We compared the mean heart rates and pause rates of the 2.3 and 4 hour observation periods with that of the longer 16 hour monitoring. The results of this analysis are as outlined in the table below.

Conclusions: There was significance in the number of pauses between the various times. There would still be a role for treadmill exercise stress testing in hospitals where facilities for CT calcium scanning are not available.

Griin dressing post cardiac catheterization: traditional pressure versus 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.

Design: An experimental design, randomized study.

Patients: 80 post cardiac catheterization patients were randomized to have their groin dressed either with pressure dressing (N=40) or TFD (N=40). Patients am-
bulated 8 hours after the procedures. Outcome variables were hematoma forma-
tion 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 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).
Conclusions: Dressing of the puncture site after cardiac catheterization with
TFD was more comfortable than the conventional pressure dressing without any dif-
ferent in hematoma or bleeding complications. So TFD can be used safely and
comfortably after achieving hemostasis.

P4375
PCI in very elderly patients suffering an ACS
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There are few data on safety and outcomes of percutaneous coronary
revascularization (PCI) in very elderly patients suffering an Acute
Coronary Syndrome (ACS), especially those aged ≥ 85 years old.
From September to December 2011, a total of 108 very elderly patients were
admitted at our coronary care unit with a diagnosis of ACS; 44% of these (n = 48)
underwent to PCI. The average age at intervention was 86.9 years. The main
underlying causes were severe chronic renal failure (25%) and COPD (13%).
Most of the procedures (47%) was performed for acute myocardial infarction with
ST-segment elevation (STEMI), 43% for an acute coronary syndrome without ST-
segment elevation with high-risk clinical features.
Coronary angiography was performed in 45% of cases with a radial approach.
The rate of procedural failure was quite high, with about 20% of PCI ineffective:
this finding could be consistent with the high percentage of patients with severe
causal coronary artery disease (CAD).
Complication rate in this population of ultra-elderly was 25%, with a mortality rate
of 12.5%, almost entirely attributable to STEMI (63%, n=5). The cause of death
was attributed in four patients to mechanical complications of myocardial infarc-
tion; in two other patients the cause of death was an arrhythmic event. The only
complication attributable to revascularization was an acute contrast nephropathy,
which resolved during the hospital stay. Non-fatal complications consist of two
cases of severe bleeding and five cases of severe heart failure; a matter of par-
ticular concern was the low use of intra aortic counterpulsation balloon pump: in
fact, only one patient was assisted with IABP, compared with nine cases of severe
heart failure.
Our study highlighted how in very elderly patients experiencing an ACS, PCI is
a safe procedure, with a single complication attributable to the revascularization
procedure, i.e a case of acute contrast nephropathy. With regard to other compli-
cations these are mainly correlated to the underlying disease, especially acute
myocardial infarction with ST-segment elevation. Careful nursing assessment,
with a regular evaluation of main hemodynamic parameters and renal function.
may facilitate early recognition of hemodynamic deterioration and its better man-
agement.

P4376
Preoperative statin use and postoperative atrial fibrillation
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Background: Perioperative beta-blockade and statin therapy have been advo-
cated to reduce cardiac risk of noncardiac surgery. The current study investi-
gates the impact of statin therapy with or without aspirin on perioperative
mortality, atrial fibrillation, and morbidity in patients undergoing non-
cardiac, nonvascular surgery.
Methods and Results: A total of 1750 patients, undergoing noncardiothoracic,
nonvascular surgery were prospectively evaluated. Patients older than 18 years
who underwent an elective, nonday case, open surgical procedure were enrolled.
Electrocardiography and cardiac biomarkers were obtained 1 day before surgery,
and on days 1, 3 and 7 after surgery. Patients with atrial fibrillation were excluded.
Demographics, comorbidities, preoperative data (electrocardiography, echocar-
diography, age, weight, smoking status, laboratory tests), medications, and intraop-
ervative variables were evaluated for their association with the occurrence of perioperative
cardiovascular adverse events. Patients receiving statins were generally older
(68.7 vs 62.3 years; P <0.001) and more likely to be receiving a beta-blocker
(41.9% vs 24.4%; P<0.001). Statin use was associated with a lower unadjusted
double odds ratio of atrial fibrillation (2.2% vs 4.2%; P<0.001), myocardial infarction (3.4% vs
6.4%; P<0.001) and mortality (1.1% vs 2.4%; P<0.01). After adjustment for pa-
tient risk factors and surgery type, odds for atrial fibrillation (adjusted odds ratio

P4377
Carperitide can protect against acute kidney injury in patients with chronic kidney disease undergoing
coronary angiography
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Purpose: Acute kidney injury remains a common complication of coronary angi-
ography (CAG). Although previous study reported that carperitide can reduce renal
protective effects after CAG, this has not been a universal finding. We evalu-
ated whether carperitide can reduce renal damage after CAG using urinary Liver-
function test (L-FABP) expressed after renal ischemia which is a novel marker detecting renal injury more sensitively than the existing marker such as serum
creatinine.
Methods: We prospectively randomized 148 patients undergoing CAG who had
renal dysfunction (glomerular filtration rate (GFR) > 60 ml/min/1.73m2). Patients
were divided into receiving hydration alone (Hyd-group; n=74) and receiving
hydration plus carperitide (ANP-group; n=74). All patients were treated with
hydration for 12 hours before and after CAG. In ANP-group, carperitide (0.0125-
0.025μg/kg/min) was started for 1 hour before CAG and continued for 24 hours.

Conclusions: Prolonged intraoperative infusion of sodium chloride plus carperitide is more effective than sodium chloride alone for prophylaxis for acute kidney injury after CAG. Sodium chloride plus has no effect in reducing CIN, leading to improve-
ment of long-term prognosis of CKD patients.

P4378
Effects of community-based general practitioners-led care
for 12,846 patients with hypertension: study of cardiovascular risk intervention - hypertension
(SRCI-HTN) in China
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Background and Objectives: Hypertension is emerging as a leading cause of
cardiovascular morbidity, mortality, and disability among adults. General practit-
ioners (GPs) working in the community health service (CHS) organisations are
being positioned in the healthcare system to provide longitudinal care for hyper-
tensive patients. This study aimed to determine the efficacy of a community-
based intervention led by GPs on control of cardiovascular risk factors among
patients with hypertension in China.
Methods: DESIGN: a longitudinal, pre-post study. SETTING: 98 community
health centres (CHCs) in Guangzhou, the most urbanized city in southern China.
Multistage cluster sampling method was adopted in identifying the study sites.
The study was carried out over a 5-year period from 2007 through 2011. PAR-
TICIPANTS: 12,846 adult patients who had diagnosed hypertension; and 196
certicate-trained general practitioners. INTERVENTIONS: cardiovascular risk
reduction education; regular, long-term follow-up by general practitioners using
scheduled consultations and counselling. The intensity of medication treatment
was determined by the stratification of risk for cardiovascular disease (CVD).
OUTCOME MEASURES: the difference in change in systolic BP, diastolic BP,
triglyceride, total cholesterol, low-density lipoprotein (LDL) cholesterol, and
high-density lipoprotein (HDL) cholesterol.
Results: Sufficient data were available for 12,846 patients. The mean (SD) pa-
tient age was 52.5 (7.5) years, 53.9% were male, and the mean (SD) systo-
lic/diastolic BP was 146.1 (19.4)/84.6 (11.3) mm Hg at baseline. Several main
indicators of cardiovascular health improved over the study period: mean systolic
BP decreased from 146.1 to 135.1 mm Hg (p<0.001); mean diastolic BP de-
clined from 84.6 to 79.6 mm Hg (p<0.001); mean triglyceride level dropped from
137.6 to 30.1 mg/dl (p<0.005): mean total cholesterol fell from 96.4 to 74.8 mg/dl
(p<0.042); mean LDL cholesterol changed from 40.5 to 22.3 mg/dl (p<0.025) and
mean HDL cholesterol increased from 28.1 to 46.3 mg/dl (p<0.044).

Conclusions: This SRCI-HTN study showed that adult patients with hypertension
receiving GPs-led care in the community health centres achieved statistically and
clinically significant and sustained improvements on the cardiovascular indicators
for as long as 5 years. It demonstrated that the participation of GPs as the core in
the multi-disciplinary team to provide hypertension management care at the com-

Anxiety in patients with chronic heart failure: impact of perception of control and acceptance coping

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Purpose: The perception of lack of control has often been associated with anxiety. Studies have indicated that different coping strategies are differentially associated with mood in patients with chronic heart failure (CHF), and that maladaptive coping is generally linked to anxiety. Furthermore, it has been suggested that acceptance may potentially relieve emotional distress. The present study investigates if acceptance coping can buffer the hypothetical impact of perceived lack of control on higher degrees of anxiety. The aim is to clarify if the pattern of control, acceptance, and anxiety has relevance for nursing efforts to provide emotional support for patients with CHF.

Methods: 65 patients diagnosed with CHF in NYHA class II and III were included from a heart failure outpatient clinic. The participants filled in forms to measure illness perception (B-IPQ), coping strategies (Brief COPE), anxiety and depression (HADS).

Results: Univariate analysis revealed correlations between Perception of control and Anxiety (r = 0.35, p < 0.05) and Acceptance coping and anxiety(r = -0.27, p < 0.05). However, upon entering both Perception of control and Acceptance coping in a path-analysis with the latter as a mediator, the effect of acceptance coping on anxiety was rendered non-significant.

Conclusion: Although the results suggest that acceptance coping inserts an influence on lower degrees of anxiety in patients with CHF, this impact seems to be dependent on the perception of control. That is, perception of control has priority over acceptance in predicting anxiety in patients with CHF. Consequently, our results suggest that the primary nursing efforts for emotional support should be directed toward an enhanced sense of control.

Depressed chronic heart failure patients have impaired autonomic function

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Background: Depression is associated with increased morbidity and mortality in chronic heart failure (CHF) patients. Sympatho-vagal balance might contribute to the relationship between depression and worse CHF outcomes. The association between depression and sympathetic-vagal balance, as measured using heart rate variability (HRV), is unknown in CHF patients.

Purpose: The hypothesis of this study was that, in stable systolic CHF patients, impaired sympathetic-vagal balance would be independently related to depression and to the severity of depression.

Methods: Participants completed a 30-minute electrocardiogram for HRV analysis (resting, quiet, dimmed room, constant ambient temperature, no caffeine, smoking, alcohol, or exercise) and underwent a clinical interview for major or minor depression according to DSM-IV criteria. Low frequency to high frequency (LF/HF) ratio in the frequency domain, for predominance of sympathetic over parasympathetic activity, was the principal autonomic measure. Results were controlled for other co-variates (including age, sex, left ventricular ejection fraction, NYHA functional class, diabetes, renal function, beta-blocker dose and other psychological factors) using analysis of variance (ANCOVA). The outcomes were then subjected to multiple regression and pathway analysis.

Results: The sample comprised 45 participants, 35 males (78%), 10 females (22%), mean age 58.84 years (S.D. ± 12.43), NYHA Class I, N=14 (31%), II, N=26 (58%) and III, N=5 (11%), with mean left ventricular ejection fraction 41.22% (S.D. ± 11.08). Significant differences were found between patients with and without depression in all HRV frequency domain measures, with depression being significantly associated with decreased LF (nu) measures, increased HF (nu) measures, and a significant increase in the LF/HF (principal outcome) measure (p < 0.001). Regression analyses demonstrated depression had a direct effect on HRV. Social support had both direct and indirect effects on HRV via depression (p < 0.001).

Conclusion: In CHF patients, both minor and major depression are associated with predominant sympathetic over parasympathetic activity, a potential explanation for worse outcomes in depressed CHF patients. The apparent strong influence of social support on cardiac autonomic activity in CHF patients warrants further research.
The sicker refuse getting healthier: cardiac rehabilitation acceptance paradox

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Purpose: Early rehabilitation is a recommended early management after the acute coronary syndrome (ACS). We aimed to investigate the impact of clinical characteristics of ACS patients (pts) upon the decision to participate in early inpatient cardiac rehabilitation programme (ICR).

Methods: Consecutive pts after ACS (70% STEMI) treated with primary percutaneous coronary angioplasty were enrolled in the study. Quality of life questionnaires [EuroQol-5D with visual analogue scale(VAS)] and depression score (Beck Depression Scale) was collected at discharge from cardiology department in early inpatient cardiac rehabilitation programme (ICR). Depending on approval or refusal, pts were divided into two subgroups: i) who participated in ICR and ii) controls. Group I consisted of 96 pts [female n=25 (25.5%); mean age 56.6±7.6 years; mean BMI 28.4±1.1 kg/m², mean EF 45.7±8.6%; STEMI n=60 (62.5%); hypertension n= 59 (62.3%); diabetes n=24 (24.9%); smoking n= 43 (43.9%)]. Group II included 39 pts [female n=11 (28.2%); mean age 70.1±7.9 years; mean BMI 27.7±4.9 kg/m²; hypertension n=29 (74.4%), hypertension n=24 (61.5%), diabetes n=6 (15.4%); smoking n=18 (46.2%).

Results: Group II as compared to rehabilitation group presented with lower median values of red blood count (4.24±0.42×10¹²/μl vs. 4.53±0.39×10¹²/μl; p=0.009), hemoglobin (13.5±1.9 mg/dl vs. 14.3±1.17 mg/dl; p=0.042) and hematocrite (39.1±5.5% vs. 41.8±5.1%; p=0.0008). Controls had also higher total cholesterol (226±55 mg/dl vs. 189±50.5 mg/dl; p=0.049), LDL cholesterol (149±36.9 mg/dl vs. 124±39.2 mg/dl; p=0.021) and Gensini score (40.2±22.6 vs. 35±24.3; p=0.0187). There was a strong trend towards lower median depression level in rehabilitation group compared with control (8±8.6 vs. 12±6.8; p=0.0578).

In terms of other parameters, there were no statistically significant difference between both groups.

Conclusion: Patients who refused cardiac rehabilitation as compared to those who accepted had a worse clinical profile including angiographic and laboratory parameters. Worse red blood count can lead to underestimation of own physical abilities (and thus expected benefits) and depressive mood may be a contributing factor. Surprisingly, a higher depression level was only a poor predictor of refusal. Surprisingly, a higher depression level was only a poor predictor of refusal. Surprisingly, a higher depression level was only a poor predictor of refusal. Surprisingly, a higher depression level was only a poor predictor of refusal. Surprisingly, a higher depression level was only a poor predictor of refusal.

The difference of QOL between older and younger patients with atrial fibrillation in Japan


Introduction: The Atrial Fibrillation Effect on Quality-of-life (AFEQT) Questionnaire was developed and validated to measure the spectrum of quality of life (QOL) affected by atrial fibrillation (AF) and its treatment. We used this AFEQT questionnaire to investigate the QOL of patients with AF in Japan. In this study we compared the QOL of Japanese patients to those of Westerners, focusing on the differences in QOL between younger and older age.

Methods: 129 males (mean age 63.8±10.4 years) with AF were divided into two groups: 102 consecutive outpatients treated with AF in Japan. All have been treated with antiocoagulant therapy received the AFEQT questionnaire. The sample size was calculated to detect a difference of one SD in QOL.

Results: The Global Scores of YG and OG were 78.7±15.63 and 77.9±6.17, respectively. Significant differences were observed: the scores of Symptom (P=0.046), N.S. The scores of Symptom were 83.0±17.19 and 84.6±3±18.15 (YG and OG, respectively, P=0.566, N.S.). The scores of Daily Activities were 80.7±23.19 and 71.7±23.57 (YG and OG, respectively, P=0.00). The scores of Treatment Concern were 75.9±17.81 and 81.4±15.71 (YG and OG, respectively, P=0.046). The scores of Satisfaction were 75.7±18.75 and 75.99±18.05 (YG and OG, respectively, P=0.931). The score of Daily Activities included 20 items, which are divided to 4 domains (Symptom, Daily Activities, Treatment Concern, and Satisfaction).We investigated the overall global score and 4 domains score. The score is a 0 to 100 scale, where a score of 0 indicates the most severe symptoms or disability and a score of 100 indicates no limitation or disability.

Conclusions: Younger patients reported less impairment of daily activities and more concern about treatment in QOL than older patients in Japan. To younger patients, we should give enough information about the treatment to reduce their concern.
Clinical correlations of cognitive impairment in chronic heart failure

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Introduction: Cognitive dysfunction is known to be more common in patients with systolic heart failure than controls. The impact of heart failure severity on cerebral function remains unknown.

Methods: Fifty-three patients with systolic heart failure were included in the study. Patients have answered the Minimental Score and were classified as having normal cognition (25-30), mild (20-24) and moderate (10-19) cognitive impairment (CI). Patients have also completed quality of life scores (Kansas City Cardiomyopathy Questionnaire, Duke activity status index), and a depression score (Zung score). Clinical data (age, sex, NYHA class, six minute walk test) and left ventricular ejection fraction (LVEF) were also available.

Results: From the patients screened, only 14 (26%) had normal cognitive function, while 22 (41%) had mild and 17 (32%) had moderate CI. Cognitive dysfunction was strongly associated with sex, NYHA class and depressive symptomatology. Nine out of 11 female vs 14 out of 42 male were classified as having moderate CI (p=0.006). Patients with normal CI had lower zung score (41±11 vs 47±11 for mild CI, vs 54±9 for moderate CI, p=0.05) and higher KCCQ-overall score (57±37 vs 37±23 for mild CI, vs 31±26 for moderate CI, p<0.01). Across NYHA class deterioration, mean Minimental score decreases significantly (24±5 for NYHA I, 22±4 for NYHA II, 17±6 for NYHA III, p=0.023). LVEF, HF cause and six minute walk test did not differ significantly among the CI subcategories.

Conclusions: Cognitive dysfunction is very common in heart failure patients, affecting moderately almost one out of three HF patients. Cognitive dysfunction deteriorates along with HF deterioration and this has to be screened, especially when complex medical advice is given.

Symptom profile of hypertensive primary care patients with undiagnosed obstructive sleep apnea - a structural equation model analysis

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Purpose: To explore symptoms and characteristics associated with undiagnosed OSA in primary care patients with HT.

Methods: Cross-sectional design, 480 patients mean age 57.8 yrs (±6.7 yrs) with HT were included at 4 primary care centres in Sweden. Clinical examinations (performed by one nurse and one physician specialized in sleep medicine), and the BSAG, the Minimal insomnia symptoms scale, the Epworth sleepiness scale, the Berlin sleep apnea questionnaire were used to collect data. Physical activity was measured with validated pedometers.

Results: 71% of the men and 61% of the women had high risk for OSA. 76% of the high-risk men expressed that others were bothered by their snoring compared to 63% of the women (p<0.05). Men with high risk reported that breathing pauses had been noticed more commonly by others compared to women (p<0.05). Men who demonstrated a high risk for OSA had more dyslipidaemia (p=0.05–0.001), higher mean levels of P-Crea (p<0.001) and lower heredity of CVD (p<0.001) than women. These men also reported more days of moderate (p<0.05) and high intensity physical activity (p<0.05), but steps/day did not differ. Medication with ACE inhibitors and angiotensin receptor blockers were more common among high-risk men (p<0.001), but diuretics (p<0.001) and hypnotics (p<0.001) were more common among high-risk women. High-risk women reported moderate clinical insomnia more commonly than men (p<0.05). Difficulties initiating sleep and difficulties maintaining sleep were also more common among high-risk women compared to men, 42% vs 20% and 50% (p<0.001). The mean HADS anxiety score and the number of patients above cut-off were significantly higher among women with high risk compared to men (p<0.05). Blood pressure, arrhythmias or diabetes did not differ between the risk groups.

Conclusion: Knowledge about gender-specific symptoms, cardiovascular signs and risk factors associated with high BSAG risk might help to identify patients in need of sleep respiratory recordings.

Is increased high-sensitive troponin T associated with severity of sleep apnea syndrome?

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Purpose: With sleep apnea syndrome (SAS) being a factor for cardiovascular...
Nutritional assessment in a University Department of Cardiology

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Background: Overweight is strongly associated with risk of coronary disease. Its prevalence is very high in the Spanish population. During hospitalization, pre-specified questionnaire was inadequate in some cases, causing a mismatch between the amount of energy and nutrients offered and truly eaten. The nursing role is crucial in this aspect being described in NANDA Nursing Diagnoses. The objective of the present study was to assess compliance during hospitalization and nutritional adequacy of dietary prescription.

Methods: We performed a prospective observational study of consecutive patients in a University tertiary Hospital. Using a nutritional interview developed for this purpose, we recorded daily food intake of patients and carried out anthropometric recording weight, height and body mass index (BMI). The classification was made from overweight/obese BMI ≥ 14 pg/ml. No correlation with hsTnT, sleep and overnight respiratory parameters, CRP as well as lower GFR and daytime PCO2. However, during positive airway pressure therapy (CPAP/AutoCPAP or Adaptive Servoventilation) hsTnT decreased significantly (p = 0.046). In patients with long-term follow-up (n=10) within the study period, the decrease of hsTnT was even more pronounced (p = 0.013).

Conclusions: SAS does not lead to elevated hsTnT per se, but co-morbidities as often seen with SAS are associated with positive hsTnT. Nevertheless, treatment of SAS leads to reduction of hsTnT, especially in patients with long-term treatment.

Adherence to the Mediterranean diet reduces the likelihood of acute coronary syndromes, even among people with high anxiety rates: a case-control study

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Purpose: Adherence to the Mediterranean diet has long been associated with beneficial effects regarding cardiovascular disease, while anxiety exerts the opposite effects. The aim of the present work was to evaluate the association between adherence to the Mediterranean diet and the development of acute coronary syndrome (ACS) in participants with and without symptoms of anxiety.

Methods: During 2009-2010, 500 participants were enrolled; 250 were consecutive patients with a first ACS and 250 population-based, control subjects, matched to the patients by age and sex. Socio-demographic, clinical, psychological, dietary and other lifestyle characteristics were measured. Adherence to the Mediterranean diet and MedDietscore (theoretical range: 0-55), while trait anxiety with the Spielberger State-Trait Anxiety Inventory form Y2 (STAI-Y2, range 20-80).

Results: After various adjustments (i.e., age, sex, physical activity, BMI, smoking, alcohol consumption, family history of cardiovascular disease, hypertension, hypercholesterolemia and diabetes mellitus), each 1.55 increase of the MedDietscore was associated with 8% (95% CI: 0.88-0.98) lower likelihood of ACS and each unit increase of the STAI-Y2 with 4% (95% CI: 1.01-1.07) higher likelihood of ACS. When the sample was split according to the presence of trait anxiety, each 1.55 unit increase of the MedDietscore was associated with 8% (95% CI: 0.86-0.99) lower likelihood of having an ACS in subjects with low anxiety and 9% (0.83-0.90) lower likelihood in participants with moderate or severe anxiety.

Conclusions: The protective effect of the Mediterranean dietary pattern regarding ACS persisted even in subjects with trait anxiety, highlighting its beneficial role.

Frequency of returning to work after ST segment elevation myocardial infarction

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The aim of the study was to evaluate the occupational functioning and identify the health-related determinants of successful vocational rehabilitation in workers with a recent myocardial infarction (MI).

Material and Methods: The study group consisted of patients (pts) who under went percutaneous coronary intervention (PCI) for first acute ST-segment elevation myocardial infarction (STEMI) and who were employed before MI. We examined the demographic, clinical and angiographic characteristics of pts who returned to employment (group 1), and those who did not returned to work (group 2). The subject mental health as well as quality of life and occupational functioning were assessed by the Hospital Anxiety and Depression Scale (HADS) and Work Ability Index (WAI). All pts were observed during one year and cardiac events were analyzed.

Results: Among 268 pts (aged 39-64 years) 142 (53%) pts returned to work within 6 months, and 126 (47%) did not. The pts who returned to work after first MI were younger (mean age 49.2 vs 54.3 years), had higher level of education, self-rated health and quality of life than the pts who did not resume their occupational activity. In addition there was no difference in 1-year clinical events in those who returned to work and those who did not.

Conclusion: Age, sociopsychological and occupational factors have the strongest influence on the chance to return to work after myocardial infarction.
Hip fracture and risk of acute myocardial infarction: a nationwide study

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Background: Osteoporotic fractures are associated with increased mortality risk. However, few data are available on the risk of acute myocardial infarction (AMI) following hip fracture. Therefore, we investigated whether hip fracture increased the risk of AMI in a large, nationwide cohort study.

Methods: We obtained data from 8,758 patients diagnosed with hip fracture from 2000 to 2009 and from 4 matched controls for each patient from the Longitudinal Health Insurance Database (LHID 2000), Taiwan. Controls were matched for age, gender, comorbid disorders, and enrollment date. All subjects were followed up from the date of enrollment until AMI, death, or the end of data collection (2009). Cox’s regression model adjusted for age, gender, comorbid disorders, and medication was used to assess independent factors determining the risk of development of AMI.

Results: A total of 8,758 subjects with hip fractures and 35,032 controls were identified. Among these patients, 1,183 (257 hip fracture patients and 926 controls) developed AMI during the median 3.2 year (interquartile range, 1.4–5.8 years) follow-up period. Patients with hip fractures had a higher incidence of AMI occurrence when compared to controls (8.71/1000 person-years versus 6.82/1000 person-years). Figure exhibits the results of the log-rank test and Kaplan-Meier survival analysis. During the maximal 10-year follow-up period, the cumulative incidence of AMI was significantly higher in patients with hip fracture than controls (P = 0.001 by log-rank test). Multivariate analysis indicated that hip fracture was associated with a greater risk for AMI development (hazard ratio: 1.29, 95% confidence interval: 1.12–1.48, P = 0.001).

Conclusions: We conclude that hip fracture is independently associated with a higher risk of subsequent AMI.

Secular trends in women with acute coronary syndrome (ACS) referred to coronary artery angiography: a 15-year observation of the University Hospital Bern

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Purpose: It is suggested that the rate of young women suffering from ACS is increasing. We therefore investigated our invasive cardiology database to assess secular trends in the incidence of first ACS and CV risk factors in women classified into different age-groups over the last 15 years (1995 to 2010).

Methods: We extracted data of all women with coronary angiography between 1995 and 2010 for a first ACS event on age, presence, classification of ACS, and cardiovascular risk factors such as smoking, arterial hypertension, diabetes mellitus, dyslipidemia, family history, and obesity. In the age groups 20-49 yrs, 50-59 yrs, 60-69 yrs, 70-79 yrs, and 80-89 yrs, we calculated numbers of first ACS per year and proportion of first ACS per year with regard to the female population (according to data from the Swiss Federal Institute of Statistics) of the referring area (Cantons of BE, SO, FR, and NE). We also calculated the proportion of women with first ACS with CV risk factors. To assess temporal trends within age groups, we performed linear regressions of absolute and relative numbers of first ACS events versus time, as well as risk factors versus time.

Results: Absolute and relative time trends showed significant linear increases for all age groups for absolute as well as relative numbers of first ACS events (all p < 0.01, Figure 1). While the increase in the group of the 20-49 year old women was small in absolute and relative numbers, from 1995 to 2010 it was most 5-fold, compared to a 3- and 2-fold increase in the 50-59 yrs and 60-69 yrs age groups, respectively. The increase between 1995 and 2000 in the older age-group was most probably influenced by a change in indication with the advent of PCI. Temporal trends with regard to risk factors showed a significant increase in smoking and obesity in the 60-69 yrs age group.

Conclusions: Our results confirm that there was a small but significant increase of ACS in women which, relative to the incidence in 1995, was considerably greater than the increase in the 50-59 and 60-69 yrs age groups. Increases in first ACS in the 60-69 year old women may have been linked to increased prevalence of smoking and obesity.

Physical activity attenuates subclinical atherosclerosis in subjects with chronic spinal cord injury


Purpose: Cardiovascular diseases are the major cause of death in subjects with chronic spinal cord injury (SCI). Interestingly, SCI subjects present higher carotid intima-media thickness (IMT) than able-bodied individuals, independent of traditional cardiovascular risk factors. The present study investigated the effect of regular physical activity on carotid IMT in men with chronic (>1 year of injury) SCI.

Methods: We studied 43 SCI men with no voluntary motor activity [30 sedentary (60% isometric); 13 athletes (69% isometric); and 24 able-bodied men by clinical, anthropometric, laboratory, blood pressure and ultrasound carotid analysis. All enrolled subjects were normotensive, non-diabetics, non-smokers and non-hypertensive. Laboratory analyses performed included determination of IMT and carotid IMT measurements. The dependence of IMT on age was determined in each group of SCI men and able-bodied men using regression analysis. In addition, temporal trends within age groups, we performed linear regressions of absolute and relative numbers of first ACS events versus time, as well as risk factors versus time.

Results: Carotid IMT in SCI athletes (0.60 ± 0.30 mm) was lower than that of SCI sedentary individuals (0.70 ± 0.02 mm; p = 0.008), but higher than that of able-bodied subjects (0.49 ± 0.02 mm; p = 0.001). SCI athletes still presented lower triglycerides (45.2 ± 5.4 vs. 117 ± 33 mg/dL, p = 0.017) and C-reactive protein (0.49 ± 0.28 vs. 1.17 ± 0.39 mg/dL; p = 0.037) levels in comparison to SCI sedentary individuals. Conversely, all other studied variables were similar between the SCI groups. In addition, carotid IMT and C-reactive protein levels revealed that carotid IMT was significantly lower in SCI athletes in comparison to SCI sedentary individuals (p = 0.009).

Conclusions: Regular physical activity is associated with attenuation of subclinical atherosclerosis in subjects with SCI, independent of hemodynamic, metabolic and inflammatory factors.

Vitamin D deficiency in relation to circulating inflammatory cells and inflammatory markers among apparently healthy individuals

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Purpose: Vitamin D (VitD) insufficiency is widespread all over the world. It is also known that insufficient 25(OH)D3 (vitamin D3) alters metabolite function, that has been related with the development of various clinical disorders (i.e., osteoporosis, diabetes, cardiovascular disease (CVD)). This study aimed to evaluate the relationship between VitD deficiency and inflammatory cells and markers among apparently healthy adults.

Methods: During 2009, 490 volunteers (46–16 years, 40% male) were consecutively enrolled to the study (participation rate 85%). Biochemical analyses were performed through established procedures, after 12h fasting, and VitD (ng/mL), high-sensitive C-reactive protein (CRP, mg/dL), cystatin C (CysC, mg/L), haptoglobin (Hp, mg/dL), haemoglobin (Hb, g/dL), platelets (PLT, 10^9/L) and white blood cells (WBC, 10^9/L) were measured. Anthropometric (WBC, 10^9/L) were measured. Anthropometric characteristics were also recorded to account for potential confounders. Participants were classified in VitD sufficiency (i.e., ≥ 30 ng/mL) and VitD insufficiency (i.e., < 30 ng/mL). Logistic regression models were used to evaluate the association of inflammatory cells and biomarkers to the likelihood of having VitD insufficiency.

Results: Among participants, 25% were VitD sufficient. Participants with VitD insufficiency had higher values of CRP, CysC and Hb as compared with those with VitD sufficiency (all p < 0.05). Logistic regression models, adjusted for age, sex, sunlight exposure, family status, physical activity, body mass index and smoking, revealed a positive association between VitD insufficiency and CRP and a negative association with Hb. In particular, 1 mg/dL increase of CRP increase the odds of having VitD insufficiency 3.7 times (95% CI: 1.16–12.0). On the contrary, for every 1 g/dL increase of Hb, the odds of having VitD insufficiency decrease 27% (OR=0.73, 95% CI: 0.57–0.93).

Conclusion: The involvement of VitD in the homeostasis of CVD has been recently evaluated. Results showed that VitD deficiency is a significant risk factor.
Genetic predisposition to higher blood pressure increases coronary artery disease risk

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Hypertension is a risk factor for coronary artery disease (CAD). Recent genomewide association studies (GWAS) have identified 32 single nucleotide polymorphisms (SNPs) that are associated with higher blood pressure (BP) at genome-wide significance (p<5x10^{-8}). If elevated blood pressure is a causative factor for CAD, these variants should also increase CAD risk. Analyzing GWAS data from 22,253 CAD cases and 49,003 controls performed in the CARDIoGRAM consortium that 88% of these BP-associated SNPs were likewise positively associated with CAD, i.e., they had an odds ratio for CAD > 1, a proportion much higher than expected by chance (p<10^{-5}). The average relative CAD risk increase per each of the multiple BP-raising alleles observed in CARDiOGRAM was 3.0% for SBP-SNPs (95% confidence interval, CI), 1.8 to 4.3% and 2.9% for DBP-SNPs (95% CI, 1.7 to 4.1%). In sub-studies, individuals carrying most SBP- and DBP-related risk alleles (top quintile of a genetic risk score distribution) had 70% (95% CI, 50-94%) and 59% (95% CI, 40-81%) higher odds of having CAD, respectively, as compared to individuals in the bottom quintile. In conclusion, most BP-associated SNPs also confer an increased risk for CAD. These findings are consistent with a causal relationship of increasing BP to CAD. SNPs primarily affecting blood pressure contribute to the genetic basis of CAD.

Mitochondrial haplogroups H and J: risk and protective factors for ischemic cardiomyopathy

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Purpose: As mitochondria are the principal source of reactiveoxygen species (ROS), these organelles may play an important role in ischamiccardiomyopathy (IC) development. The mitochondrial genome may influence this disease. The aim of the present study was to test the relationship between IC development and the impact of single nucleotide polymorphisms (SNPs) in mitochondrial DNA (mtDNA) defining the mitochondrial haplogroups in a population study.

Methods: The study complied with the Declaration of Helsinki. DNA samples from 731 unrelated individuals (380 healthy controls and 351 IC patients) were analysed in this study. Haplogroup analysis for the ten major European haplogroups was performed by using the single base extension technique and by analysing in this study. Haplogroup analysis for the ten major European haplogroups was performed by using the single base extension technique and by analysing

Results: Compared to healthy controls, the prevalence of haplogroup H was significantly higher in IC patients (40.0% vs 50.4%, p-value<0.005) while the frequency of haplogroup J was significantly lower (10.8% vs 5.7%, p-value=0.015). The haplogroup frequencies for our controls did not differ substantially from those reported in previous studies that analyzed different European populations. The mitochondrial haplogroups distribution between cases and controls, stratified by the main ischemic cardiomyopathy risk factors (hypertension, diabetes and smoking) was similar in both groups. The analysis of the SNPs characterizing the European mtDNA haplogroups showed that the SNP m.14766C>T produces a non synonymous amino acid change, but the SNP m.14766C>T causes a change in cytochrome b. Furthermore, the SNP m.1098A>G, which produces a non synonymous amino acid change in NADH dehydrogenase subunit 3 (threonine-to-alanine), was found to be a protective factor (p-value=0.028).

Conclusion: Our results showed suggestive evidence for the association of the mitochondrial haplogroups H and J as risk and protective factors respectively for ischemic cardiomyopathy. Future analysis of the full sequenced mtDNA in these haplogroups and their phenotypic analysis will yield additional insights towards therapeutic targets for ischemic cardiomyopathy pathogenesis.

Prediction of ischemic events based on transcriptomic and genomic data in patients undergoing carotid endarterectomy

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Classical risk factors, including age, smoking, serum cholesterol, diabetes and blood pressure constitute the basis of present risk prediction models, but fail to identify all individuals at risk. The objective of this study was to investigate if genomic and transcriptional patterns improves prediction of ischemic events in patients undergoing carotid endarterectomy. Patients were followed for an average of 44 months and 25 ischemic events (18 ischemic strokes and 7 myocardial infarctions) occurred. Blinded leave-one-out cross-validation on Cox regression coefficients was used to assign gene expression based risk scores to each patient. When compared to classical risk factors, addition of coiled with higher blood pressure contributed to the genetic basis of CAD. 88% of these BP-associated SNPs were likewise positively associated with CAD, i.e., they had an odds ratio for CAD > 1, a proportion much higher than expected by chance (p<10^{-5}). The average relative CAD risk increase per each of the multiple BP-raising alleles observed in CARDiOGRAM was 3.0% for SBP-SNPs (95% confidence interval, CI), 1.8 to 4.3% and 2.9% for DBP-SNPs (95% CI, 1.7 to 4.1%). In sub-studies, individuals carrying most SBP- and DBP-related risk alleles (top quintile of a genetic risk score distribution) had 70% (95% CI, 50-94%) and 59% (95% CI, 40-81%) higher odds of having CAD, respectively, as compared to individuals in the bottom quintile. In conclusion, most BP-associated SNPs also confer an increased risk for CAD. These findings are consistent with a causal relationship of increasing BP to CAD. SNPs primarily affecting blood pressure contribute to the genetic basis of CAD.

Predictive factors for ischemic cardiomyopathy

Multiple single nucleotide polymorphisms (SNPs) have been identified to associate with type 2 diabetes (T2DM). If T2DM is a causal risk factor for coronary artery disease (CAD), SNPs increasing T2DM risk should also increase CAD risk.

We studied 29 common genetic variants previously associated with T2DM at a genomewide significant level (p<5x10^{-8}) in CARDiOGRAM, a genomewide data set including 29,003 CAD cases and 64,762 controls. Significant enrichment in T2DM SNPs than expected by chance displayed an odds ratio for CAD > 1 (20 out of 29, p=0.031). In fact, 10 T2DM SNPs were nominally significantly (p<0.05) associated with CAD in CARDiOGRAM, a proportion much higher than expected by chance. The average increase in CAD risk observed per individual T2DM risk allele was 1.27% (95% confidence interval, CI), 0.26-3.20%. Studying a weighted genetic risk score in a subgroup of 4000 cases and 5600 controls revealed that individuals in the highest quintile had an 18% higher risk (CI 4.3-44%) of CAD as compared to individuals in the bottom quintile of the genetic risk score. Our data indicate that multiple genetic variants associated with T2DM confer a small risk increase for CAD, strengthening the evidence that T2DM may be a causal risk factor for CAD.
Cardiovascular disease incidence and compliance on treatment strategy in patients with familial hypercholesterolemia

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Introduction: Familial hypercholesterolemics are considered high risk patients. Purpose: To evaluate the cardiovascular disease incidence and compliance on treatment strategy in patients with familial hypercholesterolemia.

Methods: We enrolled 443 consecutive patients, clinically diagnosed with heterozygous familial hypercholesterolemia (172 men), of mean age 40.4±15 years. We measured their biochemical parameters and lipid profile before and after initiation of lipid lowering therapy. We also recorded all major cardiovascular disease events during their follow-up period.

Results: Mean period of follow-up was 8 years. 26.6% of the population showed poor compliance to drug therapy. The overall cardiovascular events incidence was 8% (36 events), 16 events occurred on those who showed the poorest compliance on drug therapy and 19 events on those who followed the prescribed instructions (13.5% vs 5.8%, p<0.001). Multi-linear regression showed that increasing the follow-up period by 1 year as well as the compliance to drug therapy, the cardiovascular events decrease by 1.33%, independently of age, sex, body mass index, arterial hypertension, smoking habits, total and LDL cholesterol levels, pre-existing coronary artery disease and prescribed therapy.

Conclusion: A considerable percentage of heterozygous FH patients show poor compliance to treatment strategy and this finding consists independent prognostic factor of major cardiovascular events.

Risk factors for coronary plaque progression in patients with far east Asians - A serial volumetric IVUS analysis


Backgrounds: Far East Asians have been reported to be at lower risk of cardiovascular events than Westerners, suggesting the potential racial difference in atherosclerotic plaque progression. However, few data exist correlating cardiovascular risk factors with volumetric IVUS measurements of coronary plaque progression in Asians.

Methods: Serial volumetric IVUS examinations (baseline and 14-months follow-up, mean measured length: 43 mm) were performed for 297 Far East Asian patients with stable angina pectoris. Patients were subsequently treated with a combination of angiotension-II receptor blocking agents (ARBs), β-blockers, calcium channel blockers, glymic control agents and/or statins per physician’s guidance. Serial progression rate of atherosclerosis was compared with the patients’ characteristics during the follow-up periods.

Results: In multiple linear and logistic regression test, age >65-years, diabetes, and male gender remained as predictors of increased plaque volume by serial IVUS. On the other hand, the use of statins and ARBs were identified as factors associated with decreased plaque volume.

Conclusions: Advanced age, poorly controlled diabetes and male appear to be predictors of atherosclerotic progression in Far East Asians. Statins and angiotension-II receptor blocking agents may play a positive role in potential plaque regression of coronary arteries in this population.
require an aggressive early preventive intervention, focused on lifestyle changes, smoking cessation and medication compliance.

**RENALE DENERVATION THERAPY IN HYPERTENSION**

**P4411** One year pooled outcomes following renal sympathetic denervation in patients with resistant hypertension: From the Symplicity HTN-2 trial

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**Purpose:** Renal sympathetic nerve activation plays an important role in the pathogenesis of essential hypertension and selective ablation of the sympathetic nerves through the renal arteries can substantially reduce blood pressure (BP) in patients with treatment-resistant hypertension. The duration of antihypertensive effect and long-term safety of renal denervation (RDN) requires further follow-up.

**Methods:** This prospective, multicentre, randomised trial evaluated the safety and effectiveness of RDN in patients with an office systolic BP of ≥160 mm Hg while taking ≥3 antihypertensive medications. The control group was managed with medication alone and at 6 months after randomization were offered RDN treatment if eligibility was met. Data from all patients receiving RDN was pooled and change in BP at 6 and 12 months, pulse pressure, heart rate, and adverse events were analyzed.

**Results:** There were 89 patients treated with RDN. At 12 months post-procedure, data are available for 47 patients randomized to immediate RDN and 33 crossover patients. The mean age of patients treated was 58.6 years, 44% were female, mean body mass index was 31.1 kg/m², and mean heart rate at baseline was 73.7 bpm. Approximately one-third of patients had type 2 diabetes. There was one renal artery dissection. No other serious adverse events occurred.

**Conclusion:** The antihypertensive effect of RDN is durable to 12 months in patients with treatment-resistant hypertension. Additional data describing the effects of RDN on renal function, pulse pressure and heart rate through 12 months will be reported.

**P4412** Percutaneous renal sympathetic denervation exerts a chronic effect on renal hemodynamics using a novel catheter for radiofrequency ablation: data from an animal study

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**Purpose:** To examine whether renal sympathetic denervation, performed using a novel radiofrequency ablation catheter, exerts a chronic (1 month post ablation) effect on renal hemodynamics assessed by average peak velocity (APV), renal flow reserve (RFR), and resistive index (RI).

**Method:** In 9 anaesthetized female juvenile farm swine (mean age 6 months, mean weight 34.5 kg), a 0.014 inch Doppler flow wire was introduced in the renal artery for the measurement of the APV under baseline and hyperemic condition that was induced by the bolus intravenous administration of dopamine (50ug/kg). RFR was calculated as the ratio of hyperemic to basal peak velocity. RI was estimated as (peak systolic velocity – end-diastolic velocity)/peak systolic velocity. APV, RFR and RI were measured before and 1 month after renal sympathetic denervation. The sympathetic denervation was achieved via the lumen of the catheter connected to a radiofrequency generator from St. Jude Medical according to pre-specified algorithm.

**Results:** In all animals, APV 1 month post ablation compared to APV before ablation was significantly higher (30.2±13.4 vs 19.7±3.8 cm/sec, p<0.05). Moreover, radiofrequency ablation resulted in reduced RFR (1.36±0.25 vs 2.96±1.33, p<0.001) and RI (0.48±0.15 vs 0.74±0.07, p<0.001), while no significant changes in the diameter of the renal artery was observed after dopamine administration (p=NS).

**Conclusion:** In patients with resistant hypertension, catheter-based RDN results in an immediate and persisting reduction of systolic and diastolic BP. A slight compensation of BP reduction was observed between day one and the 3 as well as 6 months follow-ups. Thus patients susceptible to RDN-therapy seems to provide an acute and chronic therapeutic option to endagered hypertensive Patients.

**P4413** Renal sympathetic denervation - inducing an immediate and persisting blood pressure lowering effect

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Catheter-based renal sympathetic denervation (RDN) has shown to significantly reduce blood pressure (BP) in patients with severe hypertension. According to Symplicity HTN-1 and -2 trials it is known that the blood pressure lowering effect will take about 1 to 6 months to develop.

Our study carefully investigated early and subsequent blood pressure response to RDN in a cohort of patients with resistant hypertension.

**Methods and Results:** Our study enrolled 81 consecutive patients (mean age 64.4±9.8 years, 48% women). Baseline values included a mean of 5.6±1.4 antihypertensive medications.

A 24h Holter BP monitoring was recorded in every patient 24h before as well as 24h, 3 and 6 months after RDN. BP readings were then averaged according to daytime (7:00am-22:59pm), night (22:00pm-7:00am) and 24 hours intervals. In treated patients mean averaged systolic BP was reduced by 14.5±3.2 mmHg (p<0.001) during the first 24 hours. Systolic blood pressure reduction appeared to be much higher at daytime (16.2±2.50 mmHg, p<0.001) compared to night (10.61±2.47 mmHg; p<0.001) which might indicate the role of sympathetic activity at daytime. A concordant effect on diastolic BP was observed: 6.9±1.7 mmHg (p<0.001). Systolic BP reduction sustained at 3 (11.7±3.2 mmHg, p<0.001) and 6 months (9.3±3.3 mmHg, p<0.009) without further decrease – on the contrary a relapse to higher BP was seen.

**Figure 1. BP reduction (mm Hg) after RDN**

**P4414** Renal denervation for resistant hypertension: real world outcomes

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**Purpose:** Arterial hypertension is the largest single contributor to global mortal-
Renal sympathetic denervation with brachytherapy using beta-radiation catheter. Results from a feasibility and safety preclinical study

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Background: Renal sympathetic denervation using intravascular radiofrequency ablation has demonstrated significant reduction in systolic and diastolic blood pressure in clinical trials. Local radiotherapy demonstrated the ability to damage the nerve system and is currently used for the treatment of trigeminal neuralgia. This study aimed to assess feasibility and safety of a novel approach for RSD using a clinically available beta-radiation catheter beta-cath™.

Methods: Ten naive Yorkshire swine underwent intravascular brachytherapy using a β-emitting radiation source. Dosages of 25 or 50 Gy was delivered in the proximal renal artery. Animals were followed up to 1- or 2-months and were assessed by angiography, IVUS and histology. Norepinephrine levels were measured in the renal artery and in the renal tissue of the imitated kidneys.

Results: Renal artery intravascular brachytherapy was performed without any procedural complications. No thrombus formed on the catheter and no acute vessel injury was noted by angiography. All animals survived to the predetermined follow up. At 1- and 2-month follow up there was no vascular injury as documented by angiography, IVUS (Figure 1A) and histology. Histology studies showed focal hypocellular fascicles with cellular degeneration and some cells having vacuolated cytoplasm as well as mild perineural inflammation with and without fibrosis (Figure 1B). Norepinephrine levels will be available at presentation.

Conclusions: Vascular brachytherapy using the beta-cath™ system in the renal artery in the porcine model is feasible and safe with evidence of sparing damage to the nerve and safety vascular parameters even at high dose of radiation. The results of this study supports clinical evaluation of brachytherapy for the treatment of resistant hypertension.

P4418 Effect of renal sympathetic denervation on blood pressure and renal perfusion in a pig model for obstructive sleep apnea

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Objective: Obstructive sleep apnea (OSA) is associated with resistant hypertension and a progression of chronic kidney disease (CKD). Renal sympathetic innervation may contribute to either condition. We investigated the effect of renal sympathetic denervation (RDN) on blood pressure (BP), renal perfusion and neurohumoral responses during and after repetitive obstructive apneas.

Methods: Blood pressure, femoral artery and renal artery flow were measured in 22 spontaneously breathing urethane-chloralose anaesthetised pigs. In 12 pigs, the effect of RDN was investigated. Repetitive tracheal occlusions for 2 min with applied negative tracheal pressure at -80 mbar were performed over 3 hours.

Results: Spontaneous breathing attempts during tracheal occlusion caused a strongly intraespiric oscillating pattern of renal perfusion. Renal flow oscillations were more than twofold stronger with a gain between BP and renal flow of 2.9±mmHg compared with femoral flow that almost showed changes proportional to the BP-alterations (1.3±mmHg; p<0.0001). Marked postapneic hemodynamic changes – a rise in BP from 120.3±172.8±mmHg (p<0.00001) together with renal hyperperfusion falling from 190±24 to 105±20ml/min (p<0.0001) – occurred after application of tracheal occlusion. Renal sympathetic denervation inhibited postapneic BP rises and renal hyperperfusion and attenuated increased plasma renin activity and aldosterone concentration induced by repetitive tracheal occlusions. Additionally, increased urinary protein/creatinine-ratio was significantly reduced by RDN while intraespiric hemodynamic changes were not significantly modified by RDN.

Conclusion: Renal sympathetic denervation inhibits postapneic BP-rises and renal hyperperfusion and attenuates neurohumoral responses and increased protein/creatinine-ratio induced by repetitive obstructive apneas. RDN may therefore provide protection in patients with obstructive sleep apnea, hypertension and renal dysfunction.

P4417 Percutaneous renal denervation (PRD) improves central hemodynamics and arterial stiffness - a pilot study

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Background: Percutaneous renal denervation (PRD) is a novel treatment strategy for patients with resistant arterial hypertension. Since central aortic pressures and arterial stiffness are better predictors for future cardiovascular events than peripheral pressures the present study aimed at measuring central pressures and aortic stiffness parameters in patients undergoing PRD.

Methods: 27 patients (18-82 years, mean age 63.6±years) with an office systolic blood pressure of more than 150 mmHg were included. PRD was performed with an PRD radiofrequency ablation catheter system. Central aortic pressure and aortic stiffness was calculated with an oscillometric blood pressure meter.

Results: 21 patients [5±1.3 antihypertensive drugs] were randomized to PRD. 6 patients[4±2] served as controls. Central systolic blood pressure (SBP) declined significantly in the therapy group after three [156±13 vs. 145±13 mmHg; p<0.05] and six months [156±13 vs. 148±17 mmHg; p<0.05]. Likewise, central systolic downstroke (CSD) was significantly reduced. Central systolic blood pressure (SBP) declined significantly in the therapy group after three [156±13 vs. 145±13 mmHg; p<0.05] and six months [156±13 vs. 148±17 mmHg; p<0.05]. Likewise, central systolic downstroke (CSD) was significantly reduced. Central aortic blood pressure (PPV) improved significantly [three month: 10.9±1.8 vs. 9.4±1.2 mmHg; p<0.01; six month: 10.9±1.8 vs. 9.7±1.9 mmHg; p<0.01] Values did not change significantly in the control group. Univariate analysis of variance (F-test) showed a mean arterial pressure (MAP) independent improvement of PWV in the treatment group.

Conclusion: PRD significantly reduced central aortic pressures and arterial stiffness. Effects on PWV are only partially dependent on blood pressure changes. Thus, PRD may improve cardiovascular outcome beyond blood pressure effects in patients suffering from resistant arterial hypertension.

P4418 Age-dependent effects of renal denervation therapy on diastolic blood pressure and pulse pressure

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The hallmark of hypertension in the elderly is a progressive vascular dysfunction. Aging is per se associated with the deterioration in arterial compliance through both structural and functional changes in large arteries. The role of sympathetic nervous dysfunction in a larger proportion of older patients with systolic hypertension is unknown. Renal sympathetic denervation (RDN) via a percutaneous radiofrequency catheter based approach lowers blood pressure (BP) in patients with resistant hypertension. However, the effect of RDN in young vs. elderly patients has never been studied. 24 Patients were selected according to the SIM-
Pleiotropic role of angiotensin-converting-enzyme inhibitors on bone remodeling biomarkers in hypertensive subjects

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Objectives: In addition to their well-established efficacy in lowering blood pressure, angiotensin-converting enzyme inhibitors (ACE-I) have been shown to have an impact on reducing the risk of death, myocardial infarction, stroke and renal complications in patients with coronary artery disease (CAD). Some evidence suggests that high blood pressure is associated with abnormalities of calcium metabolism, leading to an increase in calcium loss and elevation of bone remodeling biomarkers: osteoprotegerin (OPN) and osteopontin (OPG), both in CAD patients and asymptomatic subjects. In our study, we analyzed the role of antihypertensive treatment on OPG and OPN in subjects without a history of CAD.

Methods: We recruited 350 subjects using a population-based approach by computer-generated randomization with general practitioners. Subjects (n=267) were considered to have hypertension because they were taking antihypertensive agents or had a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Antihypertensive drugs were used in 240 patients as a monotherapy (n=113) or in combination with two (n=95) or three (n=32) drugs. Remaining hypertensive patients (n=47) had masked (or uncontrolled) hypertension. Biochemical parameters were assessed by routine laboratory techniques. Bone remodeling biomarkers were analyzed by commercially available immunoenzymatic assays.

Results: Among analyzed subjects n=287 had defined hypertension, and n=240 of them were treated with antihypertensive drugs. We observed that both OPG and OPN levels were higher in hypertensive subjects in comparison to normotensive ones: 3.49±1.85 vs. 2.83±1.32 pmol/L (p<0.007) and 88.8±95.85 vs. 56.58±69.04 ng/mL (p=0.012). Additional analysis of antihypertensive treatment showed that there was no significant difference in OPG and OPN levels between treated and non-treated hypertensive subjects. However, the patients stratification according to the used antihypertensive drugs revealed that treatment with ACE-I alone significantly reduced OPN levels in patients compared to treated patients with other hypertensive drugs: 79.40±88.72 vs. 139.29±124.48 ng/mL (p=0.013), or those treated with ACE-I in combination with another drug: 73.8±64.21 vs. 108.0±94.65 ng/mL (p=0.018). OPN levels were predicted in hypertensive subjects by diabetes and ACE-I treatment, but not by age or body mass index: β=0.17 (p=0.005) and β=0.14 (p=0.017), respectively.

Conclusions: Angiotensin blockade inhibits OPG expression in hypertensive asymptomatic subjects, but this mechanism does not involve OPG axis. Combinant therapy does not impair the effect of ACE-I on OPN levels.

The Effect of sRAGE in inhibiting Angiotensin Converting-enzyme mediated Atherosclerosis in Apolipoprotein E deficient mice

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Background: The activation of the renin-angiotensin system (RAS)-signaling is a contributing factor for the development of atherosclerosis. Previous studies have shown that activation RAS is associated with increased expression of the Receptor for Advanced Glycation Endproducts (RAGE) at the site of vascular inflammation. The cross talk between RAGE and angiotensin II (AngII) activation may be important in the development of atherosclerosis. Soluble RAGE (sRAGE), a truncated soluble form of the receptor, acts as a decoy and prevents the inflammatory response meditated by RAGE activation. In this study, we sought to determine the effect of sRAGE in inhibiting AngII induced atherosclerosis in apolipoprotein E knockout mice.

Methods and Results: 9 week old ApoE KO mice were infused subcutaneously with AngII (1 μg/min/kg) and saline for 4 weeks using osmotic mini-pumps. The mice were divided into 4 groups. Mice infused with saline group, mice infused with saline and sRAGE IP injection for 4 weeks. Mice infused with AngII group, mice infused with saline and sRAGE IP injection for 4 weeks. The concentration of sRAGE was varied from 0.5 μg, 1 μg, 2 μg/day for each group to determine the dose response. We show that atherosclerosis in the AngII infused ApoE KO mice was increased by over 2.5-fold compared to the ApoE KO mice. The treatment of 0.5 μg, 1 μg SAGE in AngII group resulted in the decrease in atheroma plaque area by 35%. In addition, the treatment with 2 μg of sRAGE resulted in 70% decrease in atheroma plaque area in the AngII group.

Conclusion: The results prove that blockade of RAGE activation by sRAGE prevents AngII-induced atherosclerosis. The results from this study suggest that first, RAGE activation is a strong predictor of cerebrovascular, cardiovascular, and renal disorders. Second, as AngII activation is a major pathway in the development of atherosclerosis, the results from this study may provide the basis for future anti-atherosclerotic drug development mediated through RAGE activation.

Renal denervation therapy in hypertension / Renin–angiotensin–aldosterone system in hypertension

P4419

P4420

Cardiovascular protection by BAY 94-8862, a novel non-steroidal mineralocorticoid receptor antagonist in a preclinical model of hypertension and diastolic heart failure

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Purpose: High aldosterone levels especially in combination with increased salt intake inappropriately activate the mineralocorticoid receptor (MR). Blockade of this MR activation has shown to be an invaluable therapy in heart failure. Renal impairment is an important co-morbidity of heart failure and application of available steroidal MR antagonists to this group of patients is limited. We aimed to investigate the efficacy of a novel non-steroidal MR antagonist, BAY 94-8862 vs. the steroidal MR antagonist eplerenone in a preclinical model of salt-dependent hypertension and diastolic heart failure.

Methods: Uninephrectomized male SD rats were given 1% NaCl in drinking water and subcutaneous injections of deoxycorticosterone acetate (DOCA, 30 mg/kg
once weekly) for 10 weeks. The animals were treated with vehicle or three doses of BAY 94-8862 (0.1, 1 and 10 mg/kg/day) and two doses of eplerenone (30 and 100 mg/kg/day) by once daily gavage (n=7-12/group). Systolic blood pressure was measured by the tail cuff method during the treatment period of the study. At the end of the experiment, hemodynamic function was measured in the left ventricle by a Millar-Tip (SF) catheter. Plasma samples were taken for subsequent pro-BNP analysis. Organ weights were determined and tissue samples were harvested for histological characterization and gene expression profiling.

Results: BAY 94-8862 significantly (p < 0.05) decreased cardiac and renal hypertrophy as assessed by pro-BNP, and expression of several renal profibrotic and remodeling biomarker genes (PAI-1, MCP-1, osteopontin, MMP-2) vs. placebo at 1 mg/kg without significant blood pressure reduction. There was a significant reduction (p < 0.05) in blood pressure, proteinuria, an improvement in diastolic function (relaxation time, tau) and decreased cardiac hypertrophy at 10 mg/kg BAY 94-8862 vs. 100 mg/kg eplerenone. In contrast, eplerenone significantly reduced blood pressure proteinuria at 30 and 100 mg/kg, but reduced pro-BNP only at 100 mg/kg and did not show an influence on the relative heart weight. Histopathological analysis of hearts and kidneys confirmed the more pronounced end organ protective activity of BAY 94-8862 versus eplerenone.

Conclusion: The novel MR antagonist BAY 94-8862 showed a pronounced cardiorenal protective in the DOCA/salt model. Cardiac hypertrophy, release of plasma pro-BNP and expression of profibrotic and remodeling biomarker genes were without impact at a dosage which line to no effect on pressure (BP). Much higher dosages of eplerenone were needed to demonstrate end organ protection in this preclinical model.

Predicting factors of adequate response in spironolactone-treated resistant hypertension
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Background: Primary aldosteronism (PA) is common among patients with resistant hypertension (RHTN). The aldosterone-to-renin ratio (ARR), which screens for PA, is expensive, and service patients in our government-run tertiary care facility cannot afford to pay for the test. The aldosterone antagonist spironolactone has been shown to reduce blood pressure (BP) in patients with RHTN, even in those without biochemical evidence of aldosterone excess. Without the benefit of an ARR testing, we sought to determine predictors of response to spironolactone (defined as systolic BP reduction ≥ 10 mmHg) among patients with RHTN.

Methods: This was an analytical cross-sectional study of patients with RHTN referred to the Hypertension Clinic of our tertiary, government run, resource-limited institution from January 2008 to November 2011. Patient demographics, clinical data, medication use, and laboratory tests were evaluated.

Results: Data from 94 patients with RHTN were included in the analysis. Mean age was 54.6±13.1 years, and 60.1% were females. The mean body mass index was 25.3±5.3 with 30.8% of patients overweight or obese. The average systolic BP reduction on addition of spironolactone was 38.7 mmHg among responders. Multiple logistic regression analysis revealed that concomitant diuretic use (thiazides and/or loop) predicted response to spironolactone (p=0.0409). Age, gender, family history of hypertension, body mass index, BP, serum potassium level at baseline, and estimated glomerular filtration rate did not predict treatment response.

Conclusion: Among patients with RHTN who did not undergo ARR testing, concomitant diuretic use predicted treatment response to spironolactone.

Effects of telmisartan on adiponectin and Retinol-Binding Protein 4 in patients with type 2 diabetes
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Background and aims: Adiponectin and Retinol-Binding Protein 4 is secreted by adipose tissue and may play a role in cardiovascular disease and insulin resistance. Telmisartan is an angiotensin receptor blocker originally developed for the treatment of hypertension. It can also partially activate peroxisome proliferator-activated receptor (PPAR-γ), which may improve insulin sensitivity. This effect may prove useful in hypertensive patients with insulin resistance or diabetes mellitus. We examined adiponectin and Retinol-Binding Protein 4 levels in patients with type 2 diabetes who treatment with the angiotensin receptor blocker telmisartan.

Methods: A total of 188 patients with hypertension and diabetes mellitus were assessed at baseline and following 24 weeks treatment with Angiotensin receptor blocker telmisartan (final dose, 80 mg). Adiponectin and Retinol-Binding Protein 4 levels were measured in plasma by radioimmunoassay.

Results: Adiponectin levels were inversely correlated with systolic (SBP; r = 0.640, P < 0.05) and diastolic (DBP; r = -0.350, P < 0.05) blood pressure at baseline and following treatment with telmisartan. Retinol-Binding Protein 4 levels were correlated with systolic (SBP; r = 0.117, P < 0.05) and diastolic (DBP; r = 0.150, P < 0.05) blood pressure at baseline and following treatment with telmisartan. There was a significant increase in adiponectin levels (0.98% confidence interval [CI], 0.57 to 1.80) microg/mL, P = 0.01) and decrease in Retinol-Binding Protein 4 levels (5.88% confidence interval [CI], 3.28 to 10.10) microg/mL, P < 0.01.

Conclusion: Adiponectin and Retinol-Binding Protein 4 levels is correlated with blood pressure in patients with type 2 diabetes. Increased adiponectin and decreased Retinol-Binding Protein 4 are associated with treatment by telmisartan. Given the growing diabetes epidemic, telmisartan that can simultaneously block the angiotensin II receptor and partially activate PPAR-γ have the potential to treat both hemodynamic and biochemical features of insulin resistance.

Blood pressure reduction with aliskiren in outpatients with hypertension in real life during 2-year follow-up. Results of the prospective 3A Registry
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Background: Little prospective data exist about blood pressure control with the new direct renin inhibitor aliskiren in daily practice.

Methods: The non-interventional 3A Registry included outpatients in whom the physician had decided to initiate or modify antihypertensive therapy in patients not achieving blood pressure control or where a modification was required for other reasons (e.g. adverse events or drug intolerance). Patients were recruited into 3 groups: treatment with the direct renin inhibitor aliskiren, an ACE-inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) or antihypertensive agents not blocking the renin-angiotensin system (RAS), alone or on top of existing antihypertensive regimens. Patients were prospectively followed for two years.

Results: Overall 9592 patients (68% with aliskiren, 18% with ACE-I/ARB, 14% without RAS-blockade) recruited by 899 physicians in Germany in 2008 and 2009 had 2-year follow-up. Patients with the aliskiren based regimen had significantly higher baseline blood pressure, more cardiovascular co-morbidities, a higher
phytochemical drugs are the new progress in the coronary artery calcification and ECG pattern of left all experimental animals. PP 30 mg/kg had the least blood pressure parameters (Fig. 1). There were not 24 hours. The largest hypotensive effect of VAL was recorded at the dose of 20 mm Hg (p=0.002-0.003) respectively. The hypotensive effect was still present in hours, the SBP and DBP were decreased by 18-22 mm Hg (p=0.007) and 15-19 mm Hg (95% CI: -8.6, 0.2), and -6.6 mm Hg (95% CI: -9.3, -3.2) mm Hg, respectively. At week 12. The effects of DAPA and HCTZ on mean SBP were similar during the daytime. Night time mean SBP did not differ between DAPA and PBO, and was lower for HCTZ than DAPA. Mean changes from baseline in GFR at week 12 were -2.9% (95% CI: -6.8, 1.2), -10.8% (95% CI: -14.8, -6.7), and -3.4% (95% CI: -7.3, 0.6) mL/min/m² for subjects receiving PBO, DAPA, and HCTZ, respectively.

Conclusions: DAPA was associated with a reduction in 24-h mean SBP, which was somewhat less than that observed with HCTZ. While reductions in daytime mean SBP were similar with DAPA and HCTZ, the change in night time mean systolic BP with DAPA was not different from PBO, and was less than with HCTZ. Small mean decreases in GFR were noted with all treatments, which were somewhat greater with DAPA than PBO and HCTZ.

P4427 Phytochemical drugs are the new progress in the genetically determined arterial hypertension treatment

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Purpose: We compared the hypotensive effect of valsartan (VAL) and polyphenol complex (PP) and, also, we assessed the efficacy of combination consisting of VAL and PP.

Methods: Male spontaneously hypertensive rats (SHR) (n=34, weight 240-280 g) were selected for study. The experimental animals were given VAL at the doses of 5 mg/kg, 10 mg/kg and 20 mg/kg and PP at the doses of 10 mg/kg, 30 mg/kg and 100 mg/kg. The combinations of VAL plus PP at the doses of VAL 5 mg/kg plus PP 30 mg/kg, VAL 10 mg/kg plus PP 30 mg/kg, VAL 20 mg/kg plus PP 50 mg/kg were tested in animals. The systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were recorded with the non-invasive blood pressure monitor NIBP 8 (Columbus Instruments, USA).

Results: Our results showed the most effective dose of PP is 30 mg/kg. In 3 hours, the SBP and DBP were decreased by 18-22 mm Hg (p=0.007) and 15-19 mm Hg (p=0.002-0.003) respectively. The hypotensive effect was still present in 24 hours. The largest hypotensive effect of VAL was recorded at the dose of 20 mg/kg. The reduction was about 20 mm Hg (p=0.003) in the SBP and 15 mm Hg (p=0.009) in the DBP. The SHR rats which were given the combination of VAL 10 plus PP 30 mg/kg had the least blood pressure characteristics (Fig. 1). There were no any statistically significant differences in the HR prior and after administration in all experimental animals.

Conclusions: The current study demonstrated the same efficacy of VAL 20 mg/kg and PP 30 mg/kg on blood pressure characteristics. In combination the dose of VAL can be lowered in half. It will allow reaching the target blood pressure with minimal side effects caused by VAL. We propose another mechanism of action of polyphenol complex irrelevant with the AT1 receptors inhibition.

P4429 Haemodynamic effects of dapagliflozin versus hydrochlorothiazide in subjects with type 2 diabetes mellitus

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Purpose: Sodium-glucose co-transporter 2 (SGLT2) reabsorbs glucose and sodium in the renal proximal tubule. Dapagliflozin (DAPA), an inhibitor of this transporter, targets hyperglycaemia in type 2 diabetes mellitus (T2DM) by increasing renal glucose excretion. The haemodynamic profile associated with administration of DAPA remains incompletely characterised. We therefore compared the effects of DAPA and hydrochlorothiazide (HCTZ) on 24-h blood pressure (BP) and glomerular filtration rate (GFR).

Methods: In this randomised, placebo-controlled, double-blind trial, 75 subjects with T2DM aged 18-70 years (y), HbA1c 6.6%-9.5%, and seated systolic BP (SBP) 130-165 mm Hg/diastolic BP 80-105 mm Hg, on a stable dose of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and no other antihypertensive medications were randomly assigned to placebo (PBO), DAPA 10 mg/day, or HCTZ 25 mg/day. Change from baseline in 24-h arterial BP and GFR, measured by iohexol clearance, was compared with baseline after 12 weeks of treatment.

Results: Subjects’ mean age was 56 years (y), T2DM duration 6.3 y, and HbA1c 7.5%. Treatment with PBO, DAPA, or HCTZ resulted in changes from baseline in 24-h arterial mean SBP of -0.9 mm Hg (95% CI: -4.2, 2.4), -3.3 mm Hg (95% CI: -6.8, 0.2), and -6.6 mm Hg (95% CI: -9.9, -3.2) mm Hg, respectively. At week 12. The effects of DAPA and HCTZ on mean SBP were similar during the daytime. Night time mean SBP did not differ between DAPA and PBO, and was lower for HCTZ than DAPA. Mean changes from baseline in GFR at week 12 were -2.9% (95% CI: -6.8, 1.2), -10.8% (95% CI: -14.8, -6.7), and -3.4% (95% CI: -7.3, 0.6) mL/min/m² for subjects receiving PBO, DAPA, and HCTZ, respectively.

Conclusions: DAPA was associated with a reduction in 24-h mean SBP, which was somewhat less than that observed with HCTZ. While reductions in daytime mean SBP were similar with DAPA and HCTZ, the change in night time mean systolic BP with DAPA was not different from PBO, and was less than with HCTZ. Small mean decreases in GFR were noted with all treatments, which were somewhat greater with DAPA than PBO and HCTZ.

P4430 Coronary artery calcification and ECG pattern of left ventricular hypertrophy or myocardial ischemia identify different healthy subjects

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Purpose: To improve risk stratification several markers have been proposed. Both the presence of coronary artery calcification (CAC), and ECG pattern of left ventricular hypertrophy/myocardial ischemia have been shown to provide prognostic information. In this study we investigated the association between traditionally risk factors, ECG-measurements and presence of CAC.

Method: A random sample of healthy males and females aged 50 or 60 years were invited to the screening study. Traditional risk factors were measured. ECG analysis included 1) left ventricular hypertrophy (LVH) using the Sokolow-Lyon criteria and the Cornell voltage x QRS duration product, and 2) myocardial ischemia based on ST segment depression and T wave inversion. A non-contrast CT scan was performed to assess the CAC score. The association between clinical variables, ECG findings, and the presence of CAC was investigated by means of multivariate logistic regression.

Results: Of 1825 invited subjects 1226 accepted the screening. The prevalence of hypertension was 50%. Hypertensive subjects frequently had LVH and/or myocardial ischemia as compared to non-hypertensive subjects (21% vs. 14% p<0.0001) as well as CAC (52% vs. 38%, p<0.0001). Results from multiple logistic regressions analyses are presented in the table.

Odds ratios for the presence of CAC

<table>
<thead>
<tr>
<th>Hypertension present</th>
<th>Hypertension absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR 95% CI P value</td>
<td>OR 95% CI P value</td>
</tr>
<tr>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
<td>3.6</td>
</tr>
<tr>
<td>50-60 years</td>
<td>2.0-4.3</td>
</tr>
<tr>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.3</td>
</tr>
<tr>
<td>3.5-6.5</td>
<td>1.8-10.5</td>
</tr>
<tr>
<td>p&lt;0.0001</td>
<td>2.4-10.5</td>
</tr>
<tr>
<td>Active smoking</td>
<td>2.2</td>
</tr>
<tr>
<td>3.0-4.3</td>
<td>1.4-4.9</td>
</tr>
<tr>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2.3</td>
</tr>
<tr>
<td>3.5-6.5</td>
<td>1.1-2.6</td>
</tr>
<tr>
<td>p&lt;0.0001</td>
<td>1.0-4.3</td>
</tr>
<tr>
<td>Family history</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0-4.3</td>
<td>0.4-1.8</td>
</tr>
<tr>
<td>p&gt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>CGC verified left ventricular hypertrophy</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0-4.3</td>
<td>0.7-1.5</td>
</tr>
<tr>
<td>CAC verified myocardial ischemia</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0-4.3</td>
<td>0.4-1.8</td>
</tr>
</tbody>
</table>

Conclusion: Patients with hypertension commonly have CAC. Despite this observation there seem to be no relationship between CAC and ECG suspected LVH and/or myocardial ischemia. Indeed, these risk markers seem to identify different subjects at risk, and together may add to better risk classification.
Five-year target systolic blood pressure less than 120 mmHg for more than 65 aged hypertension patients with chronic renal disease


Background: Many studies demonstrate that systolic blood pressure (SBP) <140 mmHg does not provide renal protection in renal disease with hypertension, but SBP <120 mmHg may be able to slow process of renal disease. However, evidence for a SBP <120 mmHg in elderly hypertension patients was recommended in Chinese hypertension guideline in 2005. The safety of SBP <120 mmHg in elderly hypertensive patients is hardly reported.

Methods: In a prospective, controlled-open-label studies, the authors have evaluated the safety and efficacy of five-year treatment on process of renal disease and risk of development of cardiovascular disease in 122 to 65 aged hypertension patients with chronic renal disease III to IV stage and macroproteinuria. Before randomization, all patients have already been treated for one-year with angiotensin converting enzyme inhibitors (ACEI) or angiotensin AT1 receptor blocker (ARBs) and other antihypertensive drugs, but their SBP are above 140 mmHg less than 150 mmHg. Blood pressure, serum creatinine (Cr) and potassium were monitored every 14 days in the period of follow-up by physician and healthcare nurse and more frequent patient-physician encounters will be improve the patients’ QoL. During the follow-up, all patients took their antihypertensive medication every day at home and adjusted their own medication according to pre-agreed rules.

Results: By the end of five year, medication possession ratio between two groups was 94% vs 94%, treatment group, despite three patients in control group died, Ccr clearance decreased from 51±2.0 to 64±3.0 ml/min (P<0.001) in the group of strict control of SBP<120 mmHg, Ccr decrease significantly from 52±1.9 to 40±2.4 ml/min (P<0.01) in the controls. During this time, urine protein excretion decreased from 1.4±0.5 to 0.2±0.3 g every 24 hours (P<0.001) in the treatment group, but urine protein excretion decreased slightly (from 1.3±0.4 to 1.2±0.6 g) (P=0.05) in the controls. Nine patients had got ACR, 11 patients stroke, 18 patients had got pneumonia, 8 patients renal dialysis and six patient died (4 in SCD and 2 in heart failure) in controls but one patient had got ACS, 4 patient had stroke, 5 pneumonia, 1 patient renal dialysis and two patients died in non-cardiac causes in the treatment group. Incidence of hyperkalaemia was similar between two groups.

Conclusions: SBP ≤120 mmHg is safe and was more apparently in decreasing proteinuria, slowing the process of renal disease and reducing the risk of development of cardiovascular events and pneumonia in elderly hypertensive patients with chronic renal disease.

P4432

Long-term, open-label treatment with triple olmesartan (Ö)/amlodipine (A)/hydrochlorothiazide (H) combination therapy in moderate-to-severe hypertension patients (pts)

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Objective: Analyse the effect of long-term, open-label treatment with O/A/H for patients with moderate-to-severe hypertension.

Design and Method: At Week 0 (baseline), pts entered a 2-week, double-blind run in during which all received dual therapy for safety and then were randomised to 8 weeks of double-blind treatment (N=2690) with different doses of O/A or O/A/H in a factorial setting. After Week 10, all pts received 8 weeks of single-blind O/A/H 20/5/12.5 mg treatment. For 36 weeks. Uncontrolled pts entered two consecutive 4-week periods of randomised, double-blind treatment that assessed the effects of up-titration to a maximum dose of O/A/H 40/5/12.5 or 40/5/25 mg. All pts then entered a 28-week, open-label titration phase in which therapy could be up- or down-titrated to O/A/H 20/5/12.5, 40/5/12.5, 40/5/25, 40/10/12.5 or 40/10/25 mg (investigator’s discretion) in order to get pts to and maintain their BP goal. This phase of the trial evaluated the safety and BP changes and seated BP goal achievement at Week 54, as well as safety and tolerability data.

Results: By Week 54, the S/BP changes were substantial and similar in O/A and O/A/H treatment groups compared with O/A. The mean S/BP was reduced from 140/90 to 130/80 mmHg (Table). Also, the mean S/BP changes were similar in all five treatment groups. The overall mean BP goal achievement rate for all pts at Week 54 was 78.1%. Each dose of triple therapy was well tolerated and overall hypertension levels were <1%.

P4433

Renoprotective effect of cilnidipine via the antioxidant activity in hypertensive patients

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Background: Cilnidipine, an L/N type calcium channel blocker (CCB), has been reported to be more beneficial on the progression of proteinuria in hypertensive patients compared with amloidepine, an L-type CCB. One of the mechanisms for this beneficial effect may be the N-type calcium channel blockade which inhibits renal sympathetic nerve activity leading to a reduction of glomerular hypertension through a vasodilation of effenter arterioles. However, the precise mechanism of the renoprotective effect of cilnidipine remains unknown. Because cilnidipine showed a significantly higher antioxidant activity than amloidepine in cultured human mesangial cells, we hypothesized that cilnidipine may have a renoprotective effect by suppressing oxidative stress in the present study.

Methods and Results: Thirty-five patients with hypertension, already receiving rennin-angiotensin system (RAS) inhibitor, were randomly assigned to cilnidipine or amloidepine: cilnidipine at a dose of 10mg/day that was increased up to a dose of 20mg/day (cilnidipine group; n=18) and amloidepine at a dose of 5mg/day that was increased up to a dose of 10mg/day (amloidepine group; n=17). After 6-months of treatment, systolic and diastolic blood pressures were significantly reduced in both groups which did not differ between them. The urinary albumin to creatinine ratio significantly decreased in the cilnidipine group after the treatment for 6 months (P<0.05) whereas it did not change in the amloidepine group. The urinary 8-hydroxy-2-deoxyguanosine (OH-DG) level (OH-DG/creatinine ratio) and liver-type fatty acid binding protein (L-FABP) level (L-FABP/creatinine ratio) decreased significantly after the treatment of cilnidipine for 6 months whereas there was no change after the treatment of amloidepine. In addition, the rates of urinary albumin, OH-DG, and L-FABP reduction were not correlated with the rate of change in systolic blood pressure.

Conclusions: The addition of cilnidipine rather than amloidepine ameliorated the...
Does obstructive sleep apnea affect the right heart in patients with resistant hypertension?

Echocardiographic study

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Purpose: There are limited data concerning the impact of obstructive sleep apnea (OSA) on the parameters of tracheal ventricle in patients with resistant systemic arterial hypertension (RSAH). The aim of the study was to determine the relationship between systolic OSA with echocardiographic parameters of right ventricle in patients with RSAH.

Methods: From 204 patients diagnosed with RSAH hypertension in REST-POL study 155 patients (88M, 62F; mean age 47.5±10.5; range 19-69yrs) with secondary hypertension were included in analysis. All patients underwent polysomnography and the apnea/hypopnea index (AHI) was calculated. Right ventricular end-diastolic area (RVAD), right ventricular end-systolic area (RVAS), main pulmonary artery dimension (MPAD), E wave velocity, systolic velocity from Doppler tissue imaging (s' RV), early diastolic velocity (e' RV) and tricuspid annular plane systolic excursion (TAPSE) were evaluated.

Results: Patients were divided into 4 groups based on AHI without OSA (AHI=0, n=43), mild OSA (AHI=15, n=45), moderate OSA (AHI 15-30, n=27), severe OSA (AHI > 30, n=40). Patients with severe OSA as compared with patients with grades of OSA had higher MPAD (26.0±2.0 vs. 21.3±1.7mm; p<0.001), RVAD (8.7±2.9 vs. 6.8±2.0cm²; p<0.01), RVAS (19.0±3.7vs. 15.0±3.6cm²; p<0.01) and AcT (114.±215.7 vs. 133.4±22.1 ms; p<0.001). There were no differences in RV systolic performance between patients with mild and without OSA. There were no differences between patients with mild or moderate OSA and without OSA in RV echo findings. AHI correlated significantly with MPAD (r=0.32; p<0.001), AcT (r=0.25; p<0.01), RVAD (r=0.27;p<0.01) and RVAS (r=0.29; p<0.01) but did not with TAPSE, s' RV and e' RV.In a multivariate models including parameters of the right heart, presence of severe OSA, gender, age, BMI and metabolic syndrome, the presence of severe OSA was independently related to MPAD (β=0.22, p<0.05) and AcT (β=0.20, p<0.05).

Conclusions: Severe OSA is an independent factor modifying right heart morphology and RV-MPAd coupling in patients with resistant hypertension.

Utility of high-sensitivity cardiac troponin T in patients undergoing elective coronary angiography

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Introduction: High-sensitivity cardiac troponin (hsTn) assays have improved diagnosis of myocardial infarction. It is unknown whether hsTn can improve the diagnosis of obstructive coronary heart disease in patients without acute coronary syndrome.

Methods: This study enrolled 1254 consecutive patients undergoing elective coronary angiography following cardiac stress testing. Obstructive coronary heart disease was defined as a stenosis ≥75% in at least one of the main native vessels or bypass grafts. Blood samples for hsTn testing were drawn on admission before coronary angiography and before cardiac stress test. A commercially available hsTn assay with a 99th percentile cut-off point of 0.014 μg/L and a limit of detection of 0.003 μg/L was used.

Results: Plasma levels of hsTn significantly correlated with the extent of coronary heart disease (r=0.14; p<0.001) but also with left ventricular ejection fraction (r=0.17; p<0.01), age (r=0.09; p<0.01), and renal function(r=0.18; p<0.001). Out of 1254 enrolled subjects, 64% had a positive stress test and 61% were diagnosed with obstructive coronary heart disease during coronary angiography. The receiver operating curve (ROC) derived optimal cut-off for the diagnosis of an obstructive coronary heart disease was 0.004 μg/L. A positive stress test result was associated with a sensitivity of 69% but only a specificity of 45% for obstructive coronary heart disease. Combining stress test results with hsTn ≥0.004 μg/L significantly improved the performance for diagnosis for obstructive coronary heart disease (c-statistics from 0.565 to 0.671; p<0.001). The sensitivity of this approach was 67% and the specificity 61%.

Conclusion: Addition of hsTn improves significantly the performance of cardiac stress testing for diagnosing obstructive coronary heart disease.

Association between increased levels of cardiac troponin before elective stenting and optical coherence tomography findings in stable angina pectoris

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Aims: With the availability of highly sensitive troponin assays, our understanding of minor myocardial damage in various cardiac conditions is challenged. Association between mild elevation of cardiac troponin I (cTnI) before percutaneous coronary intervention (PCI) in stable angina pectoris (SAP) patients and plaque morphology obtained by optical coherence tomography (OCT) was not yet elucidated. The aim of the present study is to investigate the relationship between increased levels of cTnI before elective stenting and OCT findings in SAP.

Methods and Results: We studied 180 native de novo culprit coronary lesions from 166 SAP patients who underwent OCT before elective PCI. Patients were excluded if they had significant left main disease, congestive heart failure, or renal insufficiency with a baseline eGFR < 30 ml/min/1.73m². Patients were divided into two groups according to the presence (n=28: 16%, median 0.15 ng/mL, IQR: 0.06-0.24) or absence (n=152: 84%) of cTnI > 0.010 ng/mL before PCI. Clinical and OCT findings were compared between these two groups. Thin cap fibroatheroma (TCFA) was defined as lipid-rich plaque (one or more quadrants) with fibrous cap thickness <70 μm. There were no significant differences in the clinical presentation between the two groups including inflammatory markers, eGFR, number of the diseased vessel, ejection fraction and Canadian Cardiovascular Society (CCS) grade. In quantitative coronary angiographic analysis (QCA) analysis, there were no significant differences in % diameter stenosis, lesion length, and minimum lu-
men diameter. In OCT analysis, mild cTnI elevation before PCI was associated with the presence of TCFA (8/28: 29% vs 17/152: 11%; P<0.032), smallest thinnest cap thickness (median: 65 μm (IQR: 69-120 μm) vs 107 μm (IQR: 73-140 μm); P = 0.01) and lipid quadrants (median: 3 (IQR: 2-3) vs 2 (IQR: 0-3); P < 0.001).

Post-PCI cTnI levels were greater in patients with mild baseline cTnI elevation than in those without (median: 0.52 ng/mL (IQR: 0.24 - 4.19 ng/mL) vs 0.33 ng/mL (IQR: 0.12 - 1.06 ng/mL); P=0.044).

Conclusions: Mild cTnI elevation was associated with OCT-derivable unstable plaque morphology, and may help identify SAP patients at high risk for cardiovascular injury after elective stenting.

P4439  Diagnostic performance of cardiac hybrid imaging of single photon emission computed tomography and coronary computed tomography

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Background: Although cardiac hybrid imaging of coronary computed tomography (CCT) and myocardial perfusion imaging with single photon emission computed tomography (MPI) could show the ischemic myocardial area and the culprit vessel, its clinical usefulness has not been clarified. Therefore, we evaluated the incremental clinical usefulness of the hybrid imaging in the diagnosis of coronary artery diseases.

Method: Consecutive patients (n=96) with suspected coronary artery disease who had a history of coronary artery bypass grafting (CABG) on CCT and equivocal myocardial ischemia on MPI were enrolled. We examined if the hybrid imaging would change the diagnosis on the culprit vessel of myocardial ischemia acquired by side-by-side analysis of CCT and MPI images (Table 1).

Result: In 34 (36%) of 96 patients, hybrid imaging changed the diagnosis acquired by side-by-side analysis of CCT and MPI images (Table 1). Hybrid imaging was useful to diagnose correctly the ischemic area at the border of old myocardial infarction or at postero-lateral wall that had been overlooked by side-by-side analysis.

Table 1

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The cases hybrid imaging changed the diagnosis. Changes in diagnosis from side-by-side analysis to hybrid imaging. (

Conclusion: The hybrid imaging of CCT and MPI was more useful than the side-by-side analysis for the correct diagnosis of the myocardial ischemia and its culprit vessel.

P4440 Influence of coronary plaque compositions on fractional flow reserve and epicardial stenosis resistance

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Hemodynamic effect of a coronary stenosis can be accurately determined by the assessment of fractional flow reserve (FFR) or epicardial stenosis resistance (SR). On the other hand, factors, which may potentially affect hemodynamic significance of a given coronary stenosis, such as histopathological composition of coronary plaque, are not known. The purpose of this study was to investigate the relationship between coronary plaque characteristics and hemodynamic endpoints in patients with coronary artery disease (CAD).

Methods: A Doppler and pressure sensor equipped guide wire was used for the assessment of FFR and SR in 38 coronary lesions in 38 patients. Under maximal hyperemia, SR was calculated as stenosis pressure gradient divided by average peak velocity distal to the stenosis and FFR was calculated as distal coronary pressure divided by mean aortic pressure. Compositions of coronary plaques were determined by using virtual histology intravascular ultrasound.

Results: Means of FFR and SR were 6.0 ± 0.14 and 1.66 ± 0.9 respectively. In 12 lesions, FFR was above the 0.75. In lesions with FFR value below 0.75, both FFR and SR were independently correlated with dense calcium volume (DCV) (r= -0.631, p= 0.015 and r= 0.069, p= 0.009, respectively) and necrotic core volume (NCV) (r= -0.661, p= 0.01 and r= 0.673, p= 0.008, respectively) even after controlling of plaque burden, lesion length, minimum lumen area (MLA) and MLA (external elastic membrane area). Nevertheless, in patients with intermediate stenosis (FFR >0.75), FFR and SR were not correlated with plaque characteristics.

Conclusion: For a given stenosis geometry, FFR values decreased and SR values increased with increases in DCV and NCV in patients with hemodynamically significant stenosis. This finding implies that plaque characteristics can affect hemodynamic endpoints in patients with hemodynamically significant coronary lesions.

P4441 Plasma cyclophilin A level is a novel biomarker of coronary artery disease

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Purpose: We tested our hypothesis that plasma cyclophilin A (CyPA) levels could be a novel biomarker of CAD.

Background: Oxidative stress, generated by excessive reactive oxygen species (ROS), promotes coronary artery diseases (CAD). We have recently demonstrated that ROS induces secretion of CyPA from vascular smooth muscle cells, which plays a crucial role in the pathogenesis of atherosclerosis, aortic aneurysms, and intimal thickening in mice.

Methods: In consecutive 320 patients undergoing coronary angiography, we examined the relationship between plasma CyPA levels and the severity of CAD. We measured plasma CyPA by an immunoassay based on the sandwich technique.

Results: Plasma CyPA levels were significantly higher in patients with significant coronary stenosis (>50%, n=188) compared to those without it (n=131) (P<0.001). A positive correlation was noted between plasma CyPA levels and significant coronary stenosis both univariately and even after adjustment for age, sex, hypertension, diabetes, dyslipidemia and smoking. The average number of stenotic coronary arteries and the need for coronary intervention were significantly in-dynamic in the quartiles of higher levels (both P<0.001). Indeed, plasma CyPA level was a strong predictor of CAD (adjusted odds ratio for CAD, 6.20; 95% confidence interval [CI], 3.14-12.27; P<0.001). Moreover, plasma CyPA levels were significantly correlated with the number of stenotic coronary arteries, regard-
Increased rho-kinase activity in patients with vasospastic angina after the great east Japan earthquake disaster

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Purpose: We have recently demonstrated that Rho-kinase activity in circulating neutrophils is a useful biomarker for the disease activity assessment in patients with vasospastic angina (VSA). Coronary vasospastic activity is known to be enhanced by mental/physical stress. Since we experienced the Great East Japan Earthquake in our Tohoku area on March 11, 2011, we examined whether the Rho-kinase activity was increased in VSA patients after the disaster.

Methods: In 10 patients with proven VSA, (3 patient of 32.7±4.5 years) who were hit by the earthquake/ tsunami, we examined the Rho-kinase activity in circulating neutrophils before and after the disaster as well as the influence of mental stress by using the questionnaire for post-traumatic stress disorder (PTSD).

Results: In all patients, Rho-kinase activity was increased after the disaster than before (phosphorylated myosin-binding subunit (MBS)/total MBS ratio 1.72±0.3 vs. 1.01±0.36, P<0.001), despite the continued treatment with calcium channel blockers (Figure). Among the 10 patients, 3 complained that the frequency of angina attack and the use of sublingual nitroglycerin were increased after the disaster, in whom both PTSD score (32.7±4.5) and changes in the Rho-kinase activity from the baseline (28.6±23.2% vs. 48.1±31%, P<0.05) were significantly higher than the remaining 7 patients without worsening symptoms. The changes in the Rho-kinase activity from the baseline were significantly correlated with the PTSD score (r=0.68, P<0.05).

Conclusions: These results indicate that Rho-kinase activity is enhanced in VSA patients by the disaster-related mental stress.

"Heart team" decision making in the management of patients with Coronary Artery Disease; structure, outcomes and reproducibility

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Purpose: Contemporary guidelines recommend that patients with stable angina and acute coronary syndromes (ACS) with multi-vessel disease are discussed by a multidisciplinary “Heart Team” (HT) to facilitate optimal evidence-based management. However, there is a paucity of data describing the workings of a HT, the functioning of its recommendations and the reproducibility of its decisions.

Methods: We have utilised a HT approach since 2005. We analysed the data for 2010 and describe the HT process. A random sample of cases were scrutinised to identify whether the HT decision had been implemented. Also, cases were represented after 1 year to determine consistency and reproducibility of decision making. The HT panel for the review process excluded members involved in the original discussion.

Results: During 2010, 108 meetings were held, attended by a median of 3 interventional cardiologists, 1 non-interventional cardiologist and 2 cardiac surgeons. 1454 cases were discussed (mean 13.5 cases per meeting). 854 (58.7%) were from our unit, 600 (41.3%) from referring hospitals. 356 (25.5%) were inpatients, 1096 (75%) outpatient. 1340 (92.2%) were patients with stable angina or ACS. The HT recommended coronary artery bypass grafting (CABG) ± valve surgery in 429 (32%) cases, percutaneous coronary intervention (PCI) in 303 (22.6%), and optimised medical therapy (OMT) in 264 (19.7%). In the remaining 344 cases (25.7%) further investigation was advised before a HT decision was made; most frequently a pressure wire study, in 151 cases (43.9%). Of 117 cases analysed, the HT recommendation had been fully achieved in 101 (86.3%). In the remaining 16 cases, deviation from the initial plan was due to the patient declining revascularisation (CABG 3, PCI 1), development of new comorbidity (2) or revascularisation of different vessels (6). The reason for deviation was unclear in 4 cases.

Of 50 cases re-presented, the original HT recommendation was the same in 38 (76%) cases. Different decisions in the remaining 12 (24%) included 7 cases (14%) in which further investigation had initially been suggested, and revascularisation was recommended on re-presentation.

Conclusions: A well-structured HT allows a large number of cases to be evaluated, while interdisciplinary discussion facilitates consensus with evidence-based and individualised advice. There is a prominent role for pressure wire assessment in the further evaluation of equivocal stenoses. The HT approach appears robust and reproducible in the majority of cases. Variation in decision making reflects the equipoise between suitability of CABG, PCI and OMT in many cases.

The appropriate time of intravenous hydration to prevent contrast-induced nephropathy

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Purpose: Intravenous hydration with isotonic saline for 24 hours is recommended for the prophylaxis of contrast-induced nephropathy (CIN). The aim of this study is to investigate whether the shorter infusion time is enough to prevent CIN development as compared with saline infusion for 24 hours.

Methods: 173 patients with renal dysfunction (eGFR <60ml/min/1.73m2) and elective cardiac catheterization were investigated retrospectively. Patients with standard hydration (n=118) received isotonic saline intravenously at a rate of 1ml/kg of body weight per hour for 12 hours before and after contrast administration, while those in the simple hydration group (n=55) received a total saline of 1500ml for 1 hour before and for about 8 hours after procedure. CIN was defined as an increase of 25% and over or 0.5mg/d and over in the serum creatinine concentration from baseline value.

Results: Between simple hydration group and standard hydration group, there were no differences in eGFR before contrast administration (47.6±10.8 vs. 46.9±9.8 ml/min/1.73m2, p=0.68) and contrast volume (138±26 vs. 136±30 ml, p=0.65). The total time of intravenous infusion was significantly shorter in the simple hydration group than in standard hydration group (8±1 vs. 24±0 hours, p<0.0001), but the total volume of intravenous infusion was no different in both group (1493±70 vs. 1445±351 ml, p=0.27). After contrast administration, there was no difference in the change of eGFR (0.26±4.93 vs. 1.08±4.82 ml/min/1.73m2, p=0.30). In both group, CIN developed in none of the patients.

Effective radiation dose to obtain coronary morphology and function; comparison of a non-invasive and an invasive diagnostic strategy

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Background: Diagnosis and treatment guidance of patients with suspected coronary artery disease (CAD) should rely on combined anatomic and functional data. Yet, there is growing awareness about the detrimental effect of radiation associated with diagnostic procedures.

Aim: To compare the Effective Radiation Dose (ERD) needed to obtain coronary anatomy and function by a non-invasive and an invasive diagnostic strategy.

Methods: Detailed ERD measurements were obtained during two different periods (2005, n=479; and 2010, n=207, after both the coronary computed tomography angiography and the catheter laboratory had been renewed). The non-invasive strategy consisted in the combination of the Coronary Computed Tomography Angiography (CCTA) and 99mTc-MIBI SPECT (MPI). The invasive strategy included Coronary Angiography (CA) and Fractional Flow Reserve (FFR) mea-
Novel diagnostic and therapeutic approaches in stable CAD

**P4447**

**Nearly doubled 5-year-mortality in patients with stable coronary artery disease and prior stroke in clinical practice: results of the Star-Registry**


**Background:** Patients with coronary artery disease (CAD) often have generalized atherosclerosis with additional peripheral or cerebro-vascular disease. Little is known about the impact of prior stroke on long-term outcome of patients with coronary artery disease (CAD) and stable angina in clinical practice.

**Methods:** Between Sept 2001 and March 2003, a total of 2,002 consecutive patients with AP and first angiographic diagnosis of CAD were enrolled in the STAR-Registry (50 centers). We examined the impact of prior stroke on 5-year-mortality of stable CAD in clinical practice in Germany.

**Results:** Of 2,002 patients with stable CAD, 93 patients (4.7%) had prior stroke. These patients were significantly older, more often had concomitant diseases like prior myocardial infarction, peripheral artery disease and diabetes. No differences were observed in interventional treatment at the time of enrolment as well as during the 5 year follow-up, with similar rates of PCI and CABG as compared to patients without prior stroke. Patients with prior stroke had a significantly higher 5-year-mortality (36.4% vs 18.1%, univariate analysis) as well as a higher incident stroke rate. After correction for differences in baseline characteristics and treatment using multivariate analysis, prior stroke was associated with a 47% increased 5-year-mortality of stable CAD in clinical practice (OR 1.46, 1.03-2.15).

**Conclusion:** Prior stroke was an independent predictor of 5-year outcome in stable CAD patients with a 47% increased mortality rate in clinical practice.

**P4443**

**Prognostic impact of uric acid in patients with stable coronary artery disease**

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**Background:** The association between uric acid and cardiovascular disease is poorly studied. We undertook this study to assess whether uric acid level predicts clinical outcome in patients with stable coronary artery disease (CAD) treated with percutaneous coronary intervention (PCI).

**Methods:** This study included 814 patients with stable CAD who underwent PCI. Uric acid was measured in all patients before angiography. The primary end point was 1-year mortality.

**Results:** Quartiles of uric acid were: 1.49 to <5.49 mg/dl (1st quartile; n=2034 patients), 5.49 to <6.40 mg/dl (2nd quartile; n=1981 patients), 6.40 to <7.50 mg/dl (3rd quartile; n=2093 patients) and 7.50 to 21.90 mg/dl (4th quartile; n=2043 patients). There were 196 deaths during the 1-year follow-up. The number of deaths (Kaplan-Meier estimates) according to uric acid quartiles were: 35 deaths (1.8%) in the 1st quartile, 30 deaths (1.6%) in the 2nd quartile, 45 deaths (2.2%) in the 3rd quartile and 86 deaths (4.3%) in the 4th quartile (unadjusted hazard ratio [HR]=1.60, 95% confidence interval [CI] 1.38-1.86, P<0.001 for each standard deviation [SD] increase in the logarithmic scale). Calculated for 1 mg/dl increase in the uric acid level, the unadjusted HR was 1.31 [1.23-2.40]; P<0.001, indicating a 31% increase in the unadjusted risk of 1-year mortality with each 1 mg/dl increase in the uric acid level. After adjustment for traditional cardiovascular risk factors, renal function and inflammatory status, the association between uric acid and 1-year mortality remained significant (adjusted HR=1.26, 95% CI 1.17-1.48; P<0.005 for each standard deviation SD increase in the logarithmic scale). Calculated for 1 mg/dl increase in the uric acid level, the adjusted HR was 1.15 [1.06-1.25; P=0.01] demonstrating a 15% increase in the adjusted risk for 1-year mortality for every 1 mg/dl increase in the uric acid level. Uric acid improved predictivity of the multivariable model regarding mortality (P=0.040).

**Conclusion:** In patients with stable CAD treated with PCI, elevated uric acid level predicts the increased risk of death independently from cardiovascular risk factors, status of renal function or inflammatory burden. Thus uric acid, a readily available test, has the potential to stratify the large group of patients with stable CAD in terms of mortality prediction.
Lack of concordance between image stress tests and invasive functional evaluation with pressure wire in patients with stable angina

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Background: Current guidelines suggest that coronary lesions should be treated when there is a previous ischemia stress test implying the involved myocardial area. However, sensitivity and specificity of non-invasive stress tests (NIST) can be less than expected, when compared with invasive functional invasive evaluation of lesions, using a pressure wire, particularly in patients with multivessel disease.

Purpose: To investigate the diagnostic value of NIST in patients with stable angina, compared with the invasive functional study (fractional flow reserve – FFR – evaluated with a pressure wire) during coronary angiography.

Methods: Patients with stable angina admitted for coronary angiography and with ischemia identified on a previous NIST, were included. The functional relevance of identified coronary lesions was determined by FFR evaluation (PressureWire®, St. Jude Medical), under adenosine coronary hyperemia. An FFR < 0.75 was considered as functionally significant.

Results: 57 lesions, from 36 patients (mean age 61.6±9.5 years, 24 males) were included. The NIST was myocardial perfusion scan in 29 (81%) patients and stress Echo in 7 (19%). Concordance between NIST and FFR was present in only 24 (42%) of the evaluated lesions. For the defined FFR value (0.75), NIST sensitivity was 79.0%, specificity 36.7%, positive predictive value 16.2% and negative predictive value 90%. There were no identifiable variables affecting the concordance between NIST and functional invasive evaluation (including age, gender, cardiovascular risk factors, presence of multivessel disease or ischemia affected territory). However, there was a trend for an increase in the concordance between non invasive and invasive tests when lesion where divided according to angiographic severity: for lesions < 69%, 70-89% and ≥80%, the concordance was, respectively, 29.1%, 31.0% and 100% (p=0.087).

Conclusions: NIST have a low concordance with the invasive functional evaluation of lesions with a pressure wire, usually overestimating the presence of ischemia. The lack of concordance between non invasive and invasive test tends to decrease in more severe lesions. These results should be tested in larger trials, since they might change the present recommendations for coronary lesions revascularization.

A novel method for the detection of coronary artery disease using an ultrasound sensitive microphane on the chest wall

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Background: Prior studies have associated increased amplitudes of high frequency diastolic heart sounds with Coronary Artery Disease (CAD), but these sounds are weak and difficult to identify in noisy clinical settings. The current study was inspired by the observation that the low frequency (<100 Hz) of ischaemic heart sounds are increased in CAD subjects. We tested a prototype of an acoustic system for non-invasive automated identification of coronary artery stenosis.

Methods: From an original group of 463 patients referred for elective coronary angiography we excluded those with potential confounders: arrhythmias (N=58); gender, cardiovascular risk factors, presence of multivessel disease or ischemia affected territory). However, there was a trend for an increase in the concordance between NIST and functional invasive evaluation (including age, gender, cardiovascular risk factors, presence of multivessel disease or ischemia affected territory). However, there was a trend for an increase in the concordance between non invasive and invasive tests when lesion where divided according to angiographic severity: for lesions < 69%, 70-89% and ≥80%, the concordance was, respectively, 29.1%, 31.0% and 100% (p=0.087).

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Effect of ranolazine and ivabradine on exercise stress test and on coronary and peripheral vascular function in patients with refractory microvascular angina

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Purpose: Iribadoline and ranolazine are novel anti-ischemic drugs with known beneficial effects in patients with stable angina and obstructive coronary disease. In this study we assessed their effects on exercise stress test (EST), coronary microvascular function and systemic vascular function in patients with microvascular angina (MVA).

Methods: We randomized, in a double-blind way, 46 MVA patients (defined by the presence of effort angina, positive maximal EST, normal coronary arteries at angiography and coronary flow response [CFR] to adenosine <2.5), who reported symptoms of chronic stable angina not adequately controlled by conventional antianginal therapy, to receive ivabradine (5 mg b.i.d.), ranolazine (375 mg b.i.d.) or placebo (b.i.d.) for 4 weeks. Maximal EST, CFR to adenosine and to cold pressor test (CPT) in the arm and leg were performed at baseline and after treatment.

Conclusions: There were no significant differences among groups in EST parameters, CFR to adenosine and to CPT, and FMD and NMD. Compared to placebo, time to 1 mm ST-segment depression and exercise duration were significantly improved by ranolazine (p=0.005), but not by ivabradine. No significant changes were detected in CFR to adenosine and to CPT, as well as in FMD and NMD in any group after treatment (table).

Table:
<table>
<thead>
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<th></th>
<th>Basal</th>
<th>Ranolazine</th>
<th>Placebo</th>
<th>p</th>
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<tbody>
<tr>
<td>FMD (mm/Hour)</td>
<td>0.05±6.5</td>
<td>5.19±2.2</td>
<td>3.53±2.6</td>
<td>5.62±2.8</td>
</tr>
<tr>
<td>NMD (%)</td>
<td>1.10±3.4</td>
<td>1.71±1.4</td>
<td>10.6±1.6</td>
<td>10.3±1.9</td>
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<tr>
<td>p for changes from baseline to follow-up in the 3 groups.</td>
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Conclusions: Ranolazine, but not ivabradine, was able to delay the appearance of ischemic ST-segment changes and improve exercise tolerance in MVA patients. This effect was not related to significant improvement in coronary microvascular function or in endothelial system function.

Impact of metabolic syndrome on the outcome of patients with stable coronary artery disease submitted to different types of treatment: 10-year follow-up of the MASS II trial

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Purpose: Metabolic syndrome (MetS) is understood as a condition that promotes atherosclerosis and confers an additional risk of adverse cardiovascular events in patients with coronary artery disease. The prognosis of this syndrome in this subset of patients in a long term follow up is inconclusive. Evaluate the impact of metabolic syndrome on cardiac death in patients with symptomatic chronic multivessel coronary artery disease.

Methods: Patients randomized in MASS II study submitted to coronary artery bypass surgery (CABG), angioplasty (PCI) or medical treatment (MT) were evaluated for the presence of MetS and followed prospectively for 10 years. We evaluated the incidence of overall and cardiac death in this period.

Criteria for MetS were fulfilled in 283 patients of 583 (54%) randomized to three therapeutic strategies. The presence of MetS was associated with an increased cardiac related death in studied population. During a 10-year follow-up, the probability cardiac mortality free survival was significantly different among patients in the 2 groups (MetS = 81.6% x non-MetS = 91.3% P=0.004). Stratifying patients with MetS by therapeutic approach we identify a statistical difference in cardiac death free survival comparing interventional approaches (CABG and PCI) to MT: 82.4% for CABG; 86.2% for PCI and 75.9% for MT(P=0.003). Besides, there is a group with best prognosis: patients without MetS submitted to CABG presenting 98.7% of patients free of cardiac death in a 10-year follow-up.

Conclusion: MetS confers high rates of cardiac death in patients with stable coronary artery disease irrespective of therapeutic strategy used. In patients with MetS, interventional approaches (PCI or CABG) seem to confer more protection against cardiac death in a 10-year follow-up.
YKL-40 is associated with long-term mortality in patients with stable coronary artery disease

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Objective: We investigated whether the inflammatory biomarker YKL-40 could improve the long-term prediction of death made by common risk factors plus high-sensitivity C-reactive protein (hs-CRP) and N-terminal-pro-B natriuretic peptide (NT-proBNP) in patients with stable coronary artery disease (CAD).

Background: Non-hospitalized CAD patients are usually followed in general practice. There is a need for identify biomarkers which could help to foresee the prognoses of these patients. Elevated serum YKL-40 is a short-term predictor for myocardial infarction (MI), cardiovascular mortality and all-cause mortality in patients with stable CAD.

Methods: Serum YKL-40, hs-CRP, and NT-proBNP were measured in 4265 (97.6%) of the 4372 patients with stable CAD included in the CLARICOR trial, and death was registered in a 6-years follow-up period.

Results: After adjustment for type of intervention, risk factors (age, sex, hypertension, diabetes, smoking status, and previous MI) and medical treatment (duretics, digoxin, and statin) serum YKL-40 (transformed as ln(max[82, YKL-40]/ug/L)) was significantly associated with all-cause mortality [hazard ratio (HR) = 1.55, 95% CI = 1.39-1.73, p =< 0.001]. After additional adjustment for ln(hs-CRP) and ln(NT-proBNP) this was still true [HR = 1.38, 95% CI = 1.21-1.53, p =< 0.001].

Conclusions: Serum YKL-40 is a predictor of long-term mortality in patients with stable CAD independent of common risk factors and ln(hs-CRP) and ln(NT-proBNP). Serum YKL-40 can be used for prognostication in these patients.
tion and increased cardiovascular risk. The relationship between total testos-
teron (TT) levels and extent of coronary artery disease (CAD) in patients
with chest pain and/or abnormal stress test has not been fully elucidated.

Methods: 116 subjects (mean age, 60.9 years) with stable angina and/or stress

The prevalence of refractory angina in patients
Epidemiological studies of refractory angina do not always take
into account the number of angina episodes during a certain period of time in
separate patients. The prevalence of refractory angina is not always known.

Aim of the study: To evaluate the prevalence and severity of refractory angina
in real clinical practice in patients with stable ischemic heart disease undergoing
coronary angiography.

Methods: 418 patients (30% male (72%) and 117 female (28%)) undergoing coro-

 angiography due to chronic stable angina were consecutively screened dur-

ing 1 year. Several aspects of ischemic heart disease were analyzed.

In patients with angina refractory to medical and surgical treatment followup of
chest pain episodes was recorded using standardized one-week diaries.

Results: Amongst all 418 patients 6 (1.4%) had Class I angina (CCS Angina

Grading Scale), 288 (68,9%) – Class II, 121 (28,9%) – Class III, 3 (0,7%) – Class

Conclusion: Coronary angiographic findings correlate significantly with TT lev-

els. This may reinforce the link between low testosterone and increased cardio-

vascular risk.

Markers of prognosis, incidence of sudden cardiac
dearth and failure in coronary artery disease

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Purpose: To evaluate in patients with stable angina, ST and non ST elevation
acute coronary syndrome (ACS) TT plasma levels and their impact on the outcomes
described above. The influence of TT plasma levels on the incidence of sudden cardiac
death, heart failure and other major acute cardiovascular events (MACE) for 2 years of follow up. Analytic statistic: chi square test, multiple regression.

Results: See Table.

Conclusions: Higher aggregation values of ASPItest and ADPtest, higher
plasma levels of myeloperoxidase IgG antibodies, were correlated with significant increased inci-
dence of sudden cardiac death, cardiovascular death, nonfatal AMI, heart failure and recurrent angina with readmission: significant higher incidence of left ventri-
cular systolic dysfunction in patients with acute coronary syndromes at 2 years of follow up. Endothelial dysfunction, platelets hyperactivity and oxidative stress are the
most important factors in atherosclerotic plaque instability and evolution with
major acute cardiovascular events.

Abstract P4457 - Table 1. Results at 2 years

| P4459 Excorporal shockwave myocardial
revascularization therapy (ESMR): an alternative for
patients with end-stage coronary artery disease and
chronic refractory angina pectoris?

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Purpose: Patients with chronic refractory angina complaints on maximum toler-
able medication and no further revascularization options represent a difficult therapeutic challenge. Extracorporeal Shockwave Myocardial Revascularization therapy (ESMR) might improve symptoms and alleviate ischemia by stimulating collateral growth in chronic ischemic myocardium in patients with end-stage coro-

nary artery disease. A shockwave is a single pressure pulse with a short (<1 ms) positive spike with an amplitude up to 100 MPa followed by a lower am-
plitude tensile part lasting several microseconds. The highly localized physical
forces of shockwaves increase capillary density in ischemic myocardium.

This prospective study was performed to evaluate the feasibility and safety of
ESMR.

Methods: We recruited 50 patients (40 male, mean age 66±9 years, mean left
ventricular ejection fraction 53±12%) with end-stage coronary artery disease,
chronic angina pectoris and reversible ischemia on myocardial single photon
emission tomography (SPECT). ESMR was applied to the ischemic zones (3–7 spots/session, 100 impulses/spot, 0.99 mJ/mm²) in an echocardiography-guided
and ECG-triggered fashion. The protocol included a total of 9 treatment sessions
(3 treatment sessions within one week at baseline, and after 1 and 2 months).

Exercise test, angina score (CCS class), nitrate use and SPECT 1 and 4 months
after the last treatment session were used to evaluate the effect of the ESMR.

Results: One and 4 months after ESMR, the angina complaints diminished
(CCS class 3.2±0.2 to CCS class 2.1±0.7 to CCS class 1.8±0.7, p<0.001 and
p<0.001, respectively). Sublingual nitrate use decreased (from 65% at baseline to
2.1±3.4% week to 1±2.5% week <p<0.001 and p<0.001, respectively). This clini-
cal improvement was in line with an improved myocardial uptake on stress SPECT
at 4 months follow-up (54.4±9.3% to 56.1±10.6%, p=0.023) and with an in-
crease in exercise tolerance at 1 and 4 months follow-up (from 8±2.3 to 9±2.3 to
9±6.3±8 minutes, p<0.028 and p<0.02, respectively). No clinically relevant side
effects were observed.

Conclusion: ESMR improved symptoms and reduced ischemia burden in pa-

tients with end-stage coronary artery disease. The non-invasive character of
ESMR in combination with avoidance of relative side-effects makes ESMR a
promising treatment modality for patients with chronic refractory angina pectoris.
Prognostic value of “tight” blood pressure control in patients with coronary artery disease: evidence from the Action database

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The placebo-controlled ACTION trial examined the effects of treatment with Nifedipine GITS on clinical outcomes in patients with stable symptomatic coronary artery disease. A retrospective analysis of the Action database demonstrated the importance of consistent blood pressure control (BP) to below 140/90mmHg. This further analysis evaluates the benefits of sustaining “tight” BP control, the levels recommended by current guidelines for this “high risk” patient population.

The analysis was limited to those patients who had complete BP measurements over the first year of the study (4 recordings) and excluded those who had an event during this period. The patients were then divided into 4 groups according to the proportion of visits in which BP was in control (<130/80 mmHg: <25%, 25% to <50%, 50% to <75% and ≥75%). Data were analysed for the major pre-specified ACTION outcomes by unadjusted clinical outcomes: thus, % of patients with outcome by proportion of visits with BP control. Data were also analysed estimating the hazard ratios (HR) for each outcome relative to the consistency of BP control.

Only 18.1% of patients achieved a BP control rate (<130/80 mm Hg) for more than 75% of visits and, in the first year, 46.0% were controlled at fewer than 25% of visits. With the exception of coronary angiography, the rate of all of the pre-specified cardiovascular endpoints declined as the proportion of visits with BP control increased. The risks for primary outcome (HR; 0.63; 95% CI: 0.53 to 0.75), all cardiovascular events (HR; 0.63; 95% CI: 0.53 to 0.76), myocardial infarction (HR; 0.69; 95% CI: 0.51 to 0.92), and stroke (HR; 0.34; 95% CI: 0.18 to 0.63) were less in the group with ≥75% of visits with BP control compared with the group with <25% of visits with BP control. These findings were not significantly modified when the data were analysed on the basis of two treatment groups (placebo or nifedipine GITS).

These retrospective analyses highlight the importance of the current recommendation for “tight” BP control in high-risk populations, as well as the potential benefits of sustained BP control in reducing cardiovascular endpoints.

Conclusions: Amongst all patients with stable angina undergoing coronary angiography, 6.7% had a refractory angina which is substantial. Usage of other tools apart from CCS Angina Grading Scale can help to evaluate severity of angina: standardized diaries, special tools for measurement of quality of life, etc.

Impact of coronary atherosclerosis burden on clinical presentation and prognosis of patients with coronary artery disease

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Background: The impact of coronary atherosclerosis burden on prognosis and presentation of patients with coronary artery disease (CAD) is unknown. We investigated the association of coronary atherosclerosis burden with clinical outcomes and presentation as unstable angina in patients with CAD.

Methods: This study included 10647 patients with stable (n=8149) and unstable (n=2498) CAD who underwent percutaneous coronary intervention (PCI). Coronary atherosclerosis burden was assessed by Gensini score. The primary outcome analysis was 1-year mortality.

Results: Gensini score was obtained by analysis of 13136 coronary segments. Patients were divided into groups according to quartiles of Gensini score: <13 (1st quartile; n=2650 patients), 13 to <25 (2nd quartile; n=2611 patients), 25 to <53 (3rd quartile; n=2711 patients) and ≥53 (4th quartile; n=2665 patients). The mean age in cases was 58.7 + 9.5 years, and 56.6 + 11.6 years in the control group.

Conclusions: The present study shows that CSWT application to the ischaemic areas reduced the severity of defects in the size, severity and nature of defects in the cases only. Therapy was well-tolerated by all patients.

P4463 Interleukin-6 promoter genetic polymorphism is associated with the presence and the severity of coronary artery disease

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Purpose: Interleukin 6 (IL-6) is marker of inflammatory process, closely related to the initiation and evolution of atherosclerosis. However, it remains unclear, whether common polymorphisms within the IL-6 gene affect the mechanisms of atherosclerosis. In the present study we examined the impact of the common polymorphism G-174C on IL-6 gene promoter on the severity of coronary artery disease (CAD) as well as on endothelial function.

Methods: The study population consisted of 272 patients with angiographically documented coronary artery disease (CAD) and 160 healthy controls. The G-174C polymorphism was determined by PCR and digestion with Sfani restriction enzyme. Follow-up was estimated by flow mediated dilation (FMD).

Results: The genotype distribution among the CAD patients was GG: 47.7%, GC: 30.5%, CC: 22.5%, and GG: 47.8%, GC: 43.8%, CC: 8.4% for the healthy controls. Our results showed that the CC polymorphism was associated with the presence of CAD (RR=1.11, 95% CI: 1.03-1.20, p<0.05). Importantly, the present polymorphism was also associated with the angiographic extent of CAD (X2 (1)=11.4, p<0.001). Although, the CC homozygosity was associated with lower FMD compared to the G allele carriers, this difference did not reach statistical significance.
Lipoprotein-associated phospholipase A2 (Lp-PLA2) is related with microvascular function.

Peripheral blood monocyte sirt1 expression is an important clinical implication since they demonstrate a significant association with lower risk of cardiac death in stable coronary artery disease patients: a three year follow-up

Methods: Total plasma Lp-PLA2 and HDL-Lp-PLA2 mass and activity, lipids and C-reactive protein were measured in 524 consecutive patients with stable CAD, who were followed for a median of 34 months. Primary endpoints were cardiac deaths and secondary endpoints hospitalizations for acute coronary syndrome (ACS), myocardial revascularization, arrhythmic event or stroke.

Results: Follow-up data were obtained by 477 patients. One hundred and twenty-three patients (25.8%) presented with cardiovascular events (24 cardiac deaths, 47 ACS, 28 revascularizations, 22 arrhythmic events, 2 strokes). Total plasma Lp-PLA2, HDL-Lp-PLA2 mass and activity, lipids and C-reactive protein were measured in 524 consecutive patients with stable CAD, who were followed for a median of 34 months. Primary endpoints were cardiac deaths and secondary endpoints hospitalizations for acute coronary syndrome (ACS), myocardial revascularization, arrhythmic event or stroke.

Results: Follow-up data were obtained by 477 patients. One hundred and twenty-three patients (25.8%) presented with cardiovascular events (24 cardiac deaths, 47 ACS, 28 revascularizations, 22 arrhythmic events, 2 strokes).

Conclusions: HDL-Lp-PLA2 is associated with lower risk of cardiac death in stable CAD patients, suggesting that HDL-Lp-PLA2 may significantly contribute to the antiatherogenic and cardioprotective effects of HDL.

Memory T cells are related with microvascular obstruction in ST segment acute myocardial infarction

Methods: We studied 30 patients with a first STEMI treated with percutaneous revascularization. Distinct subtypes of memory T cells: T naïve (CD45ROCD4CD62L-), T effector memory (TEM) cells (CD45ROCD4CD62L+), and chemokine receptors: CXCR3 and CCR4 were serially determined by flow cytometry before reperfusion and 24 h, 96 h and 30 days afterwards; values were compared with 33 age- and sex-matched control subjects with normal coronary arteries. Cardiac magnetic resonance was used to detect microvascular obstruction during the first week after the infarction.

Results: In comparison with controls, patients displayed more circulating TEM cells. In STEMI patients there was a significant increase of TEM cells during first 24 h compared with basal (vs 10% and vs 29% vs 142 cells/l, p<0.05). If case of TEM cells was associated with more MVO (Figure 1). An increment of TEM cells was correlated with lymphocyte trafficking after 24 hours with further TEM cells (p=0.001 in both cases).

Conclusions: Lymphocyte trafficking understood as an increase of memory T cells and chemokine receptors expression is closely related to MVO and it could be a pathophysiological mechanism to explain MVO plugging in reperfused myocardium. Further studies will be needed to determine if TEM cells number during the first stages of MI could be a useful predictor of MVO.

Update on innate and adaptive immunity in coronary artery disease

Peripheral blood monocyte sirt1 expression is reduced in patients with coronary artery disease

Methods and results: 48 male subjects admitted for cardiac catheterization were selected. The fact that patients with severe multivessel coronary artery disease (MV-CAD) remain stable for years without developing acute coronary events, while others develop myocardial infarction (MI) as the first manifestation of CAD despite mild coronary atherosclerosis remains poorly understood. We hypothesized that gene expression in peripheral blood differs in these two populations.

Methods: Whole genome microarray analysis (Illumina) was performed on peripheral-blood mononuclear cells in 3 groups: 1) patients with angiographic MV-CAD (>70% stenosis ≥ 2 vessels) but without prior MI (n=9); 2) patients with ST-elevation MI and angiographic evidence of 1-vessel disease with plaque rupture (n=14); 3) subjects with normal coronaries (NC) (n=11).

Results: Venn diagram of differentially expressed genes (FDR<0.2, 1.3 fold-change, P<0.05) demonstrated gene expression changes occurring predominately in the MV-CAD vs. NC group. These included genes of myocardial ischemia and inflammation-related genes including COX-2, EGR-1 and JUNB, pro-inflammatory cytokines (IL-1β), osteopontin (M, visfatin), and toll-like receptors (TLR4 and TLR6). The most notable finding in an Ingenuity pathway analysis was a graded enrichment in inflammation-related path-
Role of CD31 and CD38 in innate and adaptive immunity in patients with chronic stable angina and acute coronary syndromes

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Purpose: CD31 is a molecule implicated in leukocyte transendothelial migration and immunomodulation by TCR inhibition. CD31 is involved in homophilic and heterophilic binding interactions with different ligands like CD38. CD38 is a functionally pleiotropic molecule implicated in transmembrane signaling and adhesion of immune cells. Recent studies have highlighted the importance of innate and adaptive immunity in acute coronary syndrome (ACS).

Methods: We aimed to evaluate CD31 and CD38 expression by different monococyte and T-cell subsets in patients with ACS compared to chronic stable angina (SA). We also analyzed CD31 signaling in CD4+T-cells after TCR stimulation.

Results: Patients with SA had lower CD31 expression on monocyte and T-cell subpopulations as compared with SA (see Table 1). However, there were no differences in CD38 expression. Moreover, ACS patients showed a reduced TCR inhibition after stimulation with CD31 monoclonal antibodies, but there were no differences in CD38 expression.

Conclusions: In ACS, the altered CD31/CD38 expression and the reduced function of CD31 pathway suggest a defective immunomodulation which could contribute to the impaired control of inflammation. Our data also support the importance of CD31-mediated signaling in modulating low-grade inflammation in SA.

Erythrocyte aggregation portends worse outcomes in unstable angina patients undergoing percutaneous coronary interventions

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Background: We have previously reported a correlation between the time from symptom onset to the appearance of an inflammatory response and erythrocyte aggregation (EA) in the peripheral blood of acute coronary syndromes (ACS) patients. We now analyze the added prognostic value of EA determination in ACS patients undergoing percutaneous coronary interventions (PCI).

Methods: We performed an analysis on prospectively collected data at a tertiary care hospital between 2006-2011. Cox regression models were fitted for EA and C-reactive protein (CRP) cut-offs and performed separately for myocardial infarction (MI) and unstable angina pectoris (UAP) patients. Major adverse cardiovascular events (MACE) were defined as all-cause mortality, MI and stroke. Follow-up time was defined as the time form PCI to either MACE or November 20, 2011.

Results: Included were 1055 patients (837 with MI and 418 with UAP). The median follow up in the MI and the UAP groups was 14 and 15 months, respectively (maximal follow up of 4.1 years). In the MI group, elevated CRP marginally increased the risk of MACE during follow-up with either a higher or lower EA status (HR=1.9, p=0.057; HR=1.8, p=0.129, respectively) compared to patients with low CRP and low EA. In the UAP group however, there was a significant increase in MACE for the group with high CRP and high EA (HR=4.4, p<0.005) compared to the same patients. This was not found for the group with high CRP and low EA. In general, traditional risk factors as well as coronary disease severity did not predict adverse outcomes during the follow-up period.

Conclusions: Elevated EA portends worse outcomes in UAP patients undergoing PCI who present with higher CRP concentrations.

Admission white blood cell count predicts acute kidney injury in patients with acute myocardial infarction


Purpose: From the prognostic impact of baseline renal function, small increases in creatinine during hospitalization have been demonstrated to constitute an independent prognostic marker following myocardial infarction (MI). Our aim was to identify the independent predictors of in-hospital worsening renal function (WRF).

Methods: Our study population consisted of 522 patients admitted to the hospital with the diagnosis of acute MI (304 with ST-elevated MI and 218 with non-ST-elevated MI) within 12 hours of symptoms' onset. From blood sample obtained on admission white blood count, high sensitivity C-reactive protein (hsCRP), brain natriuretic peptide (BNP), troponin I (Tnl), plasma glucose and creatinine (Cr) were determined. Peak Cr levels were also measured throughout hospitalization. The MDRD equation was used to estimate glomerular filtration rate (GFR). WRF was defined as a 25% or more decrease in estimated GFR during hospital stay irrespective of any subsequent normalization of GFR. All patients enrolled underwent coroanry arteriography during in-hospital stay and the presence of underlying coronary artery disease was recorded. Ejection fraction was estimated on admission 2D echocardiography by applying the Simpson's rule.

Results: WRF was detected in 87 pts (16.7%). Patients with WRF were significantly older (by 10 years, p<0.001), more frequently females (by 16.3%, p<0.001), hypertensive (by 14.2%, p=0.032) and exhibited significantly lower diastolic blood pressure (by 4.1 mmHg, p=0.032), ejection fraction (by 8.7%, p<0.001) as well as greater prevalence of LAD involvement (by 17%, p<0.004) and less prevalent complete revascularization (by 18%, p=0.009). Additionally, although minimum GFR during hospitalization was lower in MI patients with WRF compared to those without WRF (by 1.75±1.7 vs 1.9±0.01), admission GFR levels did not differ between the study subgroups. Similarly, plasma glucose levels (by 26.5 mg/dl, p=0.025), white blood cell count (by 1497±97, p=0.024), CRP (by 18.3 g/ml, p=0.001), BNP (by 225 pg/dl, p<0.001) and Tnl levels (by 1ng/dl, p=0.025) were higher in the WRF group. In the multivariate logistic regression analysis, age (odds ratio [OR] 1.074; 95% CI 1.041 to 1.110), ejection fraction (OR 0.951; 95% CI 0.933 to 0.969) and white blood cell count (OR 1.099; 95% CI 1.004 to 1.181) turned out to be the only independent predictors of WRF.

Discussion: Admission white blood cell count, along with age and ejection fraction, predicts worsening renal failure in patients with acute MI.

Elevated plasma high sensitivity C-reactive protein and endothelin are associated with decreased flicker-light induced retinal arterial dilatation


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Purpose: High sensitivity C-Reactive Protein (CRP) and endothelin (ET) are biomarkers of cardiovascular risk in patients with and without coronary artery disease. The dynamic response of retinal vessel diameter to flicker-light is a measure of endothelial function. In this study, we sought to determine the relationship of flicker-light induced retinal arterial dilatation (Fi-RAD) with CRP and ET-1.

Methods: Patients with risk factors of atherosclerosis, with and without CAD were recruited (n=258). Fi-RAD was measured in both eyes after pupil dilation, using the Dynamic Vessel Analyzer (DVA) and expressed as percentage increase over baseline diameter in response to flicker light. CRP was measured by the rate turbidimetry method and ET-1 by radioimmunoassay method. Pearson’s correlation and linear regression analyses were used to determine the relationships.

Results: There were 119 patients (46%) with at least two atherosclerosis risk factors but no CAD, 78 patients (30%) with stable CAD and 61 patients with an acute coronary syndrome (ACS, 24%). The mean age of the total sample was...
58±11 years (mean±SD) and 175 patients were male (68%). The sample included 73% of patients with hypertension, 78% with dyslipidemia and 36% with diabetes. The BMI was 23.2±7 kg/m², total cholesterol 4.5±1.3 mmol/l, fasting glucose 6.6±2.4 mmol/l, CRP was 8.3±14.5 mg/l and ET-1 was 2.5±0.7 pmol/l (mean±SD). In the overall sample FI-RAD was inversely correlated with CRP (r=-0.13, p<0.04) and ET-1 (r=-0.16, p<0.01). For each 1 mg/L increase in CRP, FI-RAD decreased by 0.02% (95%CI -0.03, -0.01; p<0.04). For each 1 pmol/L increase in ET-1, FI-RAD decreased by 0.4% (95%CI -0.78, -0.1; p<0.01). After adjustment for age, gender, hypertension, systolic blood pressure, BMI, dyslipidemia, total cholesterol and glucose, the association between FI-RAD and CRP remained unchanged within 12-24 hours after PPCI (r²=0.8; p<0.01). However, the association between ET-1 and FI-RAD was no longer significant. In the group with ACS, only ET-1 was correlated with FI-RAD (r=0.35; p<0.01), and for each 1 pmol/L increase in ET-1 the FI-RAD decreased by 1.07% (95%CI -2.1, -0.04; p<0.04), after adjustment for the mentioned variables.

Conclusion: In patients with and without CAD, elevated CRP was associated with attenuation of retinal arteriole diameter changes to flicker light. The relationship between FI-RAD and ET-1 was only present among ACS patients. These data suggest that plasma markers of endothelial function and vascular inflammation are linked to retinal microvascular vasodilator function.

**P4472** Myocardial injury induces AIM2 inflammasome expression in neutrophil granulocytes in patients with acute coronary syndrome


**Background:** Early priming and recruitment of neutrophil granulocytes (PMN) play a crucial role in myocardial injury following acute coronary syndrome (ACS). Molecular mechanisms of PMN activation after myocardial ischemia and reperfusion remain largely unknown. In-vitro and animal studies could show that specific intracellular protein complexes, so-called inflammasomes (e.g. Nlrp3 or AIM2) can initiate an inflammatory response by sensing host-derived danger signals (DAMPs), such as ATP and other cellular components released during tissue injury. The aim of the present study was to investigate the inflammasome activation in PMN and its role in induction of the sterile inflammatory response in patients with ACS.

**Methods:** 75 patients (pts) with coronary heart disease (CHD) were included into this study. 50 pts with ACS (25 with STEMI, 25 with NSTEMI) and 25 pts with stable CHD were analyzed before and 12-24 hours after primary percutaneous coronary intervention (PPCI) or prior to elective coronary angiography, respectively. 20 healthy volunteers were enrolled as controls (Ctrl). In an in-vitro cell culture model PMN from healthy donors (n=5) were stimulated with ATP and dsDNA. Expression of the inflammasome-associated genes was analyzed using quantitative real-time PCR (relative copy number, RGN). Protein expression was quantified using Western Blot analysis.

**Results:** Expression of mRNA for AIM2 inflammasome was significantly higher in RA-patients as compared to stable CHD pts (RCN 88.1±7.7 vs. 59.4±5.4; p<0.02) or healthy controls (88.1±7.7 vs. 38.8±3.7; p<0.01). This ACS-related activation remained unchanged within 12-24 hours after PPCI (r²=0.8; p<0.0001). AIM2 expression was higher in NSTEMI than in STEMI group (84.1±4.7 and 83.5±8.1; p<0.009 and p=0.0001 vs. Ctrl). Protein expression analysis confirmed significant induction of AIM2 in STEMI (foldchange vs. Ctrl: 5.6±1.0; p<0.01). NSTEMI pts (72.5±6.6; p=0.007) and RA pts showed significantly higher expression of AIM2 downstream-target (IL-1) when compared to the STEMI group (43.7±8.2 vs. 89.7±8.6; p<0.001). In-vitro PMN stimulation with injury-associated DAMPs, dsDNA and ATP resulted in a 5-fold increase in AIM2 protein expression.

**Conclusion:** Our results identify the first time enhanced expression of AIM2 inflammasome in PMN in patients with acute coronary syndrome. Our data suggest that inflammasome activation in PMN contributes to the early ischemia-triggered inflammatory response. Measuring inflammasome activation may therefore provide a novel clinical parameter for improved diagnosis and risk assessment in patients with ACS.
Update on innate and adaptive immunity in coronary artery disease

**P4475**

**Functional characteristics of monocytes subsets in the acute and healing phases of ST elevation myocardial infarction and their effect on ejection fraction**

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**Background:** Monocytes are implicated in the pathogenesis of atherosclerotic disease from initiation of atherosclerotic plaque through to plaque instability and rupture. Little is known of the numerical and functional activity of the 3 monocytes subpopulations in the acute and healing phase post ST elevation myocardial infarction in humans.

**Method:** 96 patients (aged 64±14; 65% male) were recruited within first 24hours post percutaneous revascularization for STEMI. Peripheral blood monocyte subsets were enumerated and characterised using flow cytometry. Monocyte subsets were defined as CD14+CD16-CCR2+ (Mon1), CD14+CD16+CCR2+ (Mon2) and CD14+CD16+CCR2- (Mon3). Functional assessment of monocyte subsets was assessed by measurement of their phagocytic activity and activation of nuclear factor κ-light polypeptide gene enhancer in B-cells (NFκB) pathway using Phagocytosis Assay Kit and Flow cytometry.

**Results:** Monocyte counts were significantly higher at day 1 compared to days 10-14 (i.e. initiation of healing phase). Transh hemochoroidalangiography was performed in the first week. Monocyte subsets were enumerated and characterised using flow cytometry. Monocyte subsets were defined as CD14+CD16-CCR2+ (Mon1), CD14+CD16+CCR2+ (Mon2) and CD14+CD16+CCR2- (Mon3). Functional assessment of monocyte subsets was assessed by measurement of their phagocytic activity and activation of nuclear factor κ-light polypeptide gene enhancer in B-cells (NFκB) pathway using Phagocytosis Assay Kit and Flow cytometry.

**Conclusions:** Low MCP-1 levels are associated with decreased length of stay following CABG, whereas CRP levels (the most commonly used inflammatory marker) was quantified as an index of NFkB pathway activation using Phagocytosis Assay Kit and Flow cytometry.

**P4476**

**Inflammatory capacity of peri-coronary adipose tissue reflected by low-grade inflammation and post-operative clinical outcomes**

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**Purpose:** Patients with human immunodeficiency virus (HIV) infection have an increased risk of cardiovascular (CV) disease, though the contribution of viral infection, antiretroviral therapy (cART), and other comorbidities to these CV risk factors remains unclear. As aortic pulse wave velocity (PWV), a clinical measure of aortic stiffness, is predictive of CV risk, we sought to determine whether cART or HIV infection per se impacts PWV.

**Methods:** Patients with HIV (n=90) and controls (n=119) underwent vascular magnetic resonance imaging to assess aortic PWV between the ascending aorta and the descending aorta. Low MCP-1 levels are associated with decreased length of stay following CABG, whereas CRP levels (the most commonly used inflammatory marker) was quantified as an index of NFkB pathway activation using Phagocytosis Assay Kit and Flow cytometry.

**Results:** Patients and controls were matched for age (45 vs 44 years, p=0.65), systolic blood pressure (SBP 122 vs 119 mmHg, p=0.27), diastolic blood pressure (DBP 77 vs 78 mmHg, p=0.29), body mass index (26 vs 27kg/m², p=0.17), glucose (5.1 vs 4.9 mmol/L, p=0.21) and low density lipoprotein cholesterol (1.2 vs 0.9 mmol/L, p=0.78). HIV patients had lower high density lipoprotein cholesterol (1.4 vs 1.1 mmol/L, p<0.001), higher serum triglycerides (1.6 vs 1.0, p<0.001) and higher CRP (2.9 vs 1.1 mg/L, p<0.001). Patients with HIV had higher PWV than control subjects (6.5±2.1 vs 5.6±1.2 m/s, p<0.001). There was no difference in PWV recorded in patients on protease inhibitors (n=22) when compared to those on other forms of cART (n=66) (6.5±2.2 vs 6.4±1.9 m/s, p=0.84). Across all subjects, age (r=0.48, p<0.001), SBP (r=0.39, p<0.001), DBP (r=0.37, p<0.001), waist circumference (r=0.16, p=0.04), HIV infection (r=0.26, p<0.001), length of HIV infection (r=0.22, p<0.01) and smoking status (r=0.21, p<0.01) were all negatively correlated to PWV. There was no association between either nadir CD4 count (r=0.12, p=0.35) or viral load (r=0.19, p=0.09) and PWV. Using multivariable regression, HIV infection (β=0.7, p=0.01) and age (β=0.07, p<0.001) were both independent predictors of PWV (overall R²=0.34, p<0.001). Patients with HIV have higher PWV when compared to matched controls. HIV infection and age are both independent predictors of PWV. As PWV is predictive of CV risk, this suggests HIV infection itself may increase CV risk via its detrimental effects on aortic stiffness.

**P4477**

**Low-grade inflammation and post-operative clinical outcome in elective coronary artery bypass surgery: the emerging role of monocyte chemotactant protein 1**

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**Background:** In the post-operative phase of coronary artery disease, however, the role of background (preoperative) low-grade inflammation on clinical outcome post-cabg bypass surgery (CABG) is unclear. We explored the role of key components of low-grade inflammation such as interleukin 6 (IL-6), C-reactive protein (hsCRP) and monocyte chemotactant protein 1 (MCP-1) in clinical outcome of patients undergoing elective CABG.

**Methods:** We recruited 181 patients scheduled for elective CABG. The morning before the operation, following an 8-hours fasting period, blood samples were obtained. Patients were then followed-up until their discharge from the hospital. Results: (A) MCP-1 was increased compared to baseline, (B) but not hsCRP (C) levels were associated with increased length of hospital stay for those patients. In cox-regression, MCP-1 (as a continuous variable) was a strong predictor of the length of hospital stay (β=-0.01, independency of risk factors, Euroscore, extend of coronary artery disease and left ventricular ejection fraction preoperatively).

**Conclusions:** Low MCP-1 levels are associated with decreased length of stay following CABG, whereas CRP levels (the most commonly used inflammatory biomarker) failed to predict the length of hospitalization in these patients. These
Monocyte-derived angiogenic/reparative cells in myocardial infarction: focus on monocyte subpopulations

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Purpose: To established levels of CXCR4+ reparative monocytes and monocyte-derived endothelial progenitor cells (EPC) derived from distinct monocyte subsets in ST-elevation MI (STEMI) and non-STEMI.

Methods: CXCR4+ and CD34+KDR+ EPCs, attributable to individual monocyte subpopulations (Mon1, Mon2, Mon3), CD14+CD16+CXCR4+(Mon4) and CD14+CD16+CCR2(Mon3) were measured by flow cytometry in patients with STEMI, NSTEMI, and stable CAD (Table). Left ventricular ejection fraction (LVEF) was measured 6 weeks after STEMI onset.

Results: CXCR4+ cells derived from Mon1 and Mon2 were increased in STEMI. CXCR4+Mon2 were increased in NSTEMI. Only EPC derived from Mon3 were increased in both STEMI and NSTEMI. In STEMI CXCR4+Mon1 and CXCR4+Mon4 decreased by 1 month, with similar trend seen for Mon3-derived EPC. After adjustment for age, sex, diabetes and troponin levels only CXCR4+Mon2 (taken as average of the 4 time points) were independently predictive of LVEF (p=0.02, p=0.024).

Conclusions: Only specific monocyte subsets contribute towards upregulation of reparative and angiogenic monocytes in MI. CXCR4+Mon2 are independently associated with cardiac recovery post MI. These cells may represent a new therapeutic target in the future.

The association of neutrophil/lymphocyte ratio with coronary flow and in-hospital mace in patients with STEMI undergoing primary PCI

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Purpose: With the growing understanding of the role of inflammation in the atherosclerosis, studies have focused on hs-CRP and other inflammatory markers in the management of ST segment elevation myocardial infarction (STEMI).

This study, aimed to investigate the role of neutrophil/lymphocyte (NL) ratio and in-hospital major adverse cardiac events (MACE) in patients with STEMI undergoing primary percutaneous coronary intervention (PCI).

Methods: Four hundred and eighteen consecutive patients underwent primary PCI were enrolled to study. Patients were divided into two groups based upon the Thrombolysis In Myocardial Infarction (TIMI) flow grade score after primary PCI. High sensitive CRP and NL ratio on admission were measured.

Results: There were 185 patients (mean age 62.1±12 years and 73% male) in no-reflow group and 260 patients (mean age 59.1±13 and 81% male) in reflow group. NL ratio was significantly higher in no-reflow group compared to that of reflow group and 260 patients (mean age 59.1±13 and 81% male) in no-reflow group. NL ratio was significantly higher in no-reflow group compared to that of reflow group and 260 patients (mean age 59.1±13 and 81% male) in no-reflow group.

Conclusions: Findings suggest that MCP-1 is a sensitive inflammatory marker for risk estimation in patients undergoing CABG.
In this study, high hs CRP and MB were independent predictors of ACh induced CAS. Therefore, the more intensive antianginal treatment would be required in female pts with high hs CRP.

**Methods:** Endothelial dysfunction was assessed using a venous occlusion plethysmography. L-main unpredicted vascular response to intravenous administration of ACh. The diagnosis of ED was made if the ratio between the ACh-induced and baseline flow was decreased below 0.45.

**Results:** Among 308 patients, 92 (30%) had ED. In these subjects, an altered TH metabolism and enhanced inflammation may contribute to worse clinical outcome in patients with STEMI. LT3S is associated with a worse clinical status, a greater degree of inflammatory activation and a lower ejection fraction in patients with STEMI. In these subjects, an altered TH metabolism and enhanced inflammation may contribute to worse clinical outcome in patients with STEMI.

**Conclusions:** LT3S is an independent predictor of ACh induced CAS (OR: 1.5, p<0.01, 95% CI: 1.1-2.0), and myocardial bridge (MB) was also an independent predictor of ACh induced CAS (OR: 3.2, p<0.01, 95% CI:2.1-4.9).
A gene expression was estimated by the number of mRNA copies per one microgram of total RNA sample.

**Results:** The gene expression of TGFβ1 and its receptors in peripheral blood mononuclear cells was estimated with QRT-PCR technique in the study group patients with ACS and in the control group of healthy subjects - Table 1.

**Conclusion:** Significantly reduced gene expression of TGFβ1 and its receptors in PBMC of patients with acute coronary syndrome, compared with the high transcriptional activity in the healthy control group, confirms the protective effect of high expression of this cytokine and suggests systemic disorder in its expression as an important element of pathogenesis of acute coronary syndromes.

**P4487** Early cardiac gene transcript levels in peripheral blood mononuclear cells reflect severity in stable coronary artery disease

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**Purpose:** The early cardiac genes myocardin, GATA4 and Nkx2.5 in peripheral blood mononuclear cells (PBMCs) in patients with stable coronary artery disease (CAD) and we examined the relationship between these levels and the severity of the disease, estimated by the number of stenotic vessels involved.

**Methods:** 98 patients with stable CAD (aged 66.9±13 years) who underwent coronary angiography participated in the study. 66 healthy individuals (aged 58±13 years) were also included for comparison. Gene transcript levels were determined by quantitative real-time reverse transcription PCR.

**Results:** Patients with 3-vessel CAD had elevated transcript levels of myocardin (p<0.001, 95% CI: 1.5-5.8), GATA4 (p=0.015, 95% CI: 0.1-1.1) and Nkx2.5 (p<0.001, 95% CI: 4.5-23) compared to healthy controls. Patients with 3-vessel CAD also showed elevated transcript levels of myocardin (p<0.001, 95% CI: 0.49-5.5) and Nkx2.5 (p<0.001, 95% CI: 1.5-21.5) compared to patients with 1-vessel CAD.

**Conclusions:** Early cardiac gene transcript levels are significantly higher in PBMCs of patients with severe stable CAD than in healthy controls. Alterations in the expression profile of early cardiac genes according to the disease severity status were also observed. Our results indicate for the first time, that alterations in the early cardiac gene expression in peripheral blood of stable CAD patients, possibly reflecting alterations in circulating cardiac progenitor cells expressing these genes, may reflect the level of disease severity.

**P4488** Gamma-glutamyltransferase levels are associated with inflammatory activity, myocardial dysfunction and in-hospital mortality in patients with STElevation myocardial infarction

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**Introduction:** Gamma-glutamyltransferase (GGT) is a well known prognostic marker in patients with heart failure and stable coronary artery disease. Aim of this study is to define the relationship between GGT activity, systemic inflammation, myocardial dysfunction and in-hospital mortality in patient STElevation myocardial infarction (STEMI).

**Methods:** 1299 patients (male: 73%; mean age: 66.1±12.5 years) admitted for STEMI and undergoing early revascularization were included in the study. Routine biochemical exams, including GGT activity, fibrinogen and C-reactive protein (CRP) dosage were performed at admission. Brain natriuretic peptide BNP was determined at admission and each day during hospitalization. Ejaculation fraction was determined by echocardiography within 48 hours from admission.

**Results:** An elevation of GGT activity (>60 U/L; p<0.001) was found in 105 (8%) patients at admission. This group of subjects had also higher fibrinogen (329.5±133.9 vs 299.7±92.1 mg/dL; p<0.05), CRP (4.2±6.8 vs 1.8±3.4 mg/dL; p<0.0001), basal BNP (414.6±631.7 vs 289.4±184.6 ng/mL; p=0.04) and peak BNP levels (888.9±1403.7 vs 555.7±827.7 ng/mL; p<0.0005). A significantly lower ejection fraction was also found in these patients (42.0±10.5 vs 44.5±6.7%, p<0.01). At logistic regression analysis basal GGT activity resulted an independent predictor of in-hospital mortality (OR: 0.896; CI 0.876-0.906; p<0.0005).

**Conclusions:** Elevated GGT activity is associated with a higher degree of inflammation, neuroendocrine activation, myocardial dysfunction and in-hospital mortality in patients with STEMI. Further studies are needed to clarify whether GGT activity may be useful in predicting the development of adverse cardiac events and mortality in STEMI patients.

**P4489** Predictive incremental value of combination of inflammatory cytokines (ILS-IL10-MIG) on impaired ventricular function at discharge and on 6-month mortality after ST-elevation myocardial infarction

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**Objective:** We investigated the ability to predict left ventricular (LV) dysfunction at discharge and fatal events in 6 months of single inflammatory cytokines, and combination of cytokines measured in patients with ST-elevation acute myocardial infarction (STEMI), as first cardiovascular manifestation.

**Methods:** We studied 205 patients with STEMI randomly selected from the multi-ethnic First Acute Myocardial Infarction (FAMI) Study (1099 cases), that enrolled patients from urban area of Italy, Scotland and China. We assessed inflammatory genes measuring 14 cytokines (ILS, IL1, IL10, CRP, IL1-β, GM-CSF, VEGF, IL6, IP10, MCP, MIG, MIP1A, MIP1B, G-CSF, TNFα, and osteo) in blood obtained before reperfusion within 6 hours from symptoms onset. We had available echocardiographic estimates of LV ejection fraction (EF) at discharge data on 113 (55%) patients and complete 6-month follow-up mortality.

**Results:** At discharge 32/113 patients (28%) had LVEF below 50%, and at 6 months 12/205 patients (5.8%) were dead. We used Receiver Operating Characteristic (ROC) curves to assess the diagnostic power of GGT activity and fatal events of single cytokines and their combination. Among single cytokines IL10 (area under the curve AUC=0.65; p=0.01) was the best predictor of impaired LVEF at discharge, and IL6 (AUC=0.80, p<0.001) was the best predictor of 6-month mortality compared with any other single cytokine. Of note, within six hours from STEMI onset, when troponin I did not show any predictive value, and other clinical variable were only mildly associated with outcome (i.e. age), the combination of IL10 and MIG and IL6 reached a high predictive value both for impaired LVEF (AUC 0.71, p<0.001) and mortality (AUC 0.86, p<0.001), with a significant incremental value compared with single most predictive cytokines.

**Conclusion:** The combination of IL10, MIG and IL6 showed an incremental predictive value for LVEF impairment at discharge and 6-month mortality after STEMI, compared with single inflammatory cytokine.

**UPDATE ON CORONARY SPASM AND MICROVASCULAR DYSFUNCTION**

**P4490** The area of microvascular obstruction after acute myocardial infarction is determined mainly by infarct size and reduced clot permeability

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**Purpose:** The epicardial thrombus burden and distal macro- and microembolization are associated with perfusion deterioration during acute phase of ST-segment elevation myocardial infarction (STEMI) but their influence on microvascular obstruction remains poorly understood. We sought to investigate the quantitative impact of ex vivo measured fibrin clot properties and platelet function on microvascular obstruction (MVO) territory after primary coronary intervention (PCI).

**Methods:** Plasma clot permeability (Ks, m2, cmH2O-1) which is a measure of clot size and clot susceptibility to lysis in assays using exogenous thrombin (500, min) were prospectively assessed in 108 STEMI patients on admission (ADM) and 4 months after PCI (4M). We further assessed the association between clot properties and platelet-monocyte aggregates (PMA) with the size of MVO territory are associated with perfusion deterioration during acute phase of ST-segment elevation myocardial infarction (STEMI) but their influence on microvascular obstruction remains poorly understood. We sought to investigate the quantitative impact of ex vivo measured fibrin clot properties and platelet function on microvascular obstruction (MVO) territory after primary coronary intervention (PCI).

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Prevalence of microvascular obstruction after primary percutaneous coronary intervention is higher in male patients with hypogonadism

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Background: Testosterone deficiency afflicts approximately 30% of Men aged from 40-79 years. Recent studies claimed that androgen deficiency contributes to the onset and progression of cardiovascular disease. Microvascular obstruction (MO) is a common event associated with a worse prognosis and unfavorable left ventricular remodeling after primary percutaneous coronary intervention (P-PCI). Howeever mechanisms involved in MO have not been fully elucidated yet. We evaluated the importance of gonadal function in the onset of MO.

Methods: We studied 51 patients (59±10) men with new diagnosis of MVA. Among patients affected by MO, 39% were hypogonad (69.2%). This prevalence was significantly higher when compared to patients with normal hormonal reperfusion after P-PCI (59.6% p<0.005).

Conclusions: Androgen deficiency is associated with an higher prevalence of MO in patients with P-PCI undergoing P-PCI. Further studies are required to unveil the complete role of T in the pathogenesis of MO. T might be considered a novel diagnostic target to stratify patients with higher risk to develop MO after STEMI.

Correlation between coronary microvascular function and stable microvascular angina

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Purpose: To assess whether, in patients with microvascular angina (MVA: effort angina, positive exercise stress test [EST] and normal coronary arteries), the effects of drug therapy on angina status and quality of life (QoL) are related to changes in coronary microvascular function.

Methods: We studied 51 patients (59±10; 15 men) with a new diagnosis of MVA. Coronary blood flow response (CBFR) to adenosine and to cold pressor test (CPT). Seattle Angina Questionnaire (SAQ) and EuroQoL score for QoL were assessed at baseline, in pharmacological washout, and at 12-month follow-up under antiischemic therapy. Patients were divided into 2 groups: 1) Group 1 included patients with no improvement of QoL (EuroQoL score change <10 points); 2) Group 2 included patients with QoL improvement (increase in EuroQoL score ≥10 points). Results: Baseline, Group 1 and Group 2 had similar SAQ scores and EuroQoL score. Together with EuroQoL score, a significant improvement of SAQ scores were observed in Group 2, but not in Group 1 (Table). At 12-month follow-up the 2 groups did not differ for use of beta-blockers (27% vs. 88% in Group 1 and 2, respectively; p<0.001) whereas no differences were found for other anti- ischemic drugs. At baseline CBFR to adenosine (1.70±0.3 vs. 1.72±0.4; p=0.15) and to CPT (1.86±0.4 vs. 1.56±0.3; p=0.29) were similar in the 2 groups. At follow-up a similar significant improvement was observed in the 2 groups between both CBFR to adenosine (2.05±0.2 vs. 2.05±0.21; p=0.96) and to CPT (1.81±0.42 vs. 1.7±0.25; p=0.8).

Conclusions: In MVA patients the improvement in angina status and QoL was not related to changes in coronary microvascular function, suggesting that other features (e.g., abnormal cardiac pain sensitivity) play a significant role in the symptomatic state of patients.

Effect of short-acting nitrates on exercise stress test and coronary microcirculation in patients with microvascular angina

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Purpose: To evaluate the effects of short-acting nitrates on exercise stress test (EST) results in patients with microvascular angina (MVA) compared to patients with obstructive coronary artery disease (CAD), and to investigate the relation between EST results and coronary blood flow (CBF) response to nitrates in these patients.

Methods: We studied 54 patients with stable effort angina and known positive EST; 29 patients had angiographically normal coronary arteries (MVA), whereas 25 patients showed significant (>75%) stenosis in >1 epicardial coronary artery (CAD). Patients underwent 2 maximal treadmill ESTs on 2 separate days, in a random sequence, after withdrawing all medications: one EST without any intervention (control EST) and one EST after sublingual administration of isosorbide dinitrate, 5 mg (ISDN-EST). CBF response to nitroglycerin (25 μg) was assessed in the left anterior descending coronary artery by means of transhoracic echo-Doppler.

Results: ST-segment depression ≥1 mm (STD) at the control EST was induced in 26 (90%) and in 24 (96%) of MVA and CAD patients, respectively (p=0.41), whereas the ISDN-EST, STD was induced in 25 (86%) patients with MVA, but in only 14 (56%) patients with CAD (p=0.01). At control EST maximal STD was similar in MVA patients (1.5±0.7 vs. 1.3±0.4, respectively; p=0.07); at ISDN-EST maximal STD did not change in MVA patients, whereas it was significantly reduced in CAD patients (1.5±0.7 vs. 1.3±0.6, p=0.15 and 1.3±0.4 vs. 0.8±0.6; p=0.01, respectively). In MVA patients, rate-pressure product (RPP) at 1 mm STD at ISDN-EST and at the control EST was 2192±5438 and 208±4286 bpm·mmHg, respectively (p=0.35); the same RPP values in CAD patients were 2265±5014 and 2073±6091 bpm·mmHg, respectively (p=0.03). In MVA patients, time to 1 mm STD at ISDN-EST and at the control EST was 308±160 and 284±136 s, respectively (p=0.19); the same values in CAD patients were 474±112 and 367±163 s, respectively (p=0.01). CBF response to NTG was significantly lower in MVA compared to CAD patients (1.4±0.3 vs. 1.7±0.3; p=0.01); in MVA patients a significant correlation was found between CBF response to NTG and heart rate at STD during ISDN-EST (p=0.40; p=0.04).

Conclusions: Among patients with effort angina, short-acting nitrates improve EST results in CAD, but not in MVA patients. A lower NTG-induced coronary microvascular dilatation seems to contribute to EST positivity after nitrate administration in patients with MVA.

The index of microcirculatory resistance was strongly associated with infarct size only in anterior ST-segment elevation myocardial infarction, but not in non-anterior STEMI


Background: Previous reports showed that the index of microcirculatory resistance (IMR) after primary percutaneous coronary intervention (pPCI) for ST-segment elevation myocardial infarction (STEMI) correlated with infarct size and recovery of left ventricular function. However, the regional differences of IMR have not been well-evaluated.

Figure 1. Correlation between IMR and CK-MB AUC in anterior and non-anterior STEMI.
Objective: We investigated the correlation between IMR and infarct size in ante-
rior and non-anterior STEMI.

Method: We investigated 104 patients who underwent successful pPCI for STEMI within 12 hours after onset between April 2009 and March 2011. CK-MB was measured 1, 2, 4, 6, 9, 12, 18, 24, 48, 96 hours after pPCI, and the area under the curve of CK-MB (CK-MB AUC) was calculated as the index of infarct size. We evaluated the IMR as the quantitative index of microvascular dysfunction. After successful pPCI, IMR was measured using a PressureWireTM Certus (St. Jude Medical, USA) at maximal hyperemia.

Result: There was a significant correlation between IMR and infarct size in ante-
rior STEMI. However, this finding was not observed in non-anterior STEMI.

Conclusion: IMR may predict infarct size in only anterior STEMI, but not in non-
anteior STEMI.

P4495
Qualitative analysis of microvascular obstruction is best related to clinical prognosis than clinical markers at a 1 year follow-up: a contrast-enhanced MRI study

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Objectives: To evaluate the clinical prognostic value of a cardiac magnetic res-
sonance (CMR) assessment soon after a first STEMI segment elevation myocardial infarction (STEMI).

Background: Clinical factors such as gender, age, blood pressure, heart beat, heart and renal failure have already been described as related to poor clinical prognosis at follow-up. For now, the prognostic value and CMR param-
eters is not well-defined.

Methods: We followed for 1 year up to 168 consecutive patients with a first STEMI treated with primary angioplasty. We performed CMR at day 5±2 and 3 months to assess LV volumes. We used delayed enhanced imaging to assess the infarct size and the presence of MVO. We defined severe MVO as MVO extent being superior to its median value (2.85 gr).

Results: 13 major adverse cardiac events (MACE) including 2 cardiac deaths, 1 nonfatal myocardial infarctions, 8 readmissions for heart failure and/or stroke were documented. In univariate analysis, the MACE was related to age, creatinine peak, heart failure, MVO and LV volumes. In a complete multivariate analysis, age (hazard ratio 1.075, p=0.003), end-diastolic LV volume (HR 0.74, p=0.017), end-systolic LV volume (HR 0.74, p=0.039), MVO presence (HR 8.867, p=0.041; Log rank = 9.195, p=0.002) and severe MVO (HR 8.906, p=0.002; Log rank = 8.090, p=0.001) were the only independent prognostic variables. Of note, clinical marker such as heart failure was strongly related to age and found as non significant in multivariate analysis.

Conclusions: A comprehensive CMR assessment is useful for stratifying risk soon after STEMI; baseline LV volumes and severe MVO are the stronger inde-
pendent prognosis factor. This result supports the clinical interest of a quantitative assessment of MVO.

P4496
Coronary microvascular function is impaired in diabetic patients with normal coronary arteries and correlates to renal function

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Purpose: Endothelial dysfunction is thought to represent a common pathogenetic mechanism of impaired coronary flow reserve (CFR) and renal dysfunction in pa-
patients with type 2 diabetes mellitus (DM), yet no data are available on the relation-
ship between CFR and renal function in these patients.

Methods: In the same day, while off drugs, we studied endothelial-dependent, during cold pressure test (CPT), and independent (diprydiamole infusion (Dip) 0.84 mg/kg over 6 minutes) CFR using transthoracic Doppler echocardiography of the left descending coronary artery in 23 DM (12 men; age 62±10; and 25 non DM patients (17 men; age 61±10), matched for all other cardiovascular risk factors. Glomerular filtration rate (GFR) was estimated by Cockcroft Gault formula in the same day of CFR studies. All patients had no significant coronary artery disease (CAD) at invasive coronary angiography performed within 7 days from CFR.

Results: CPT-CFR (1.46±0.26 in DM vs 1.70±0.33 in non-DM; p=0.007) and Dip-CFR (2.38±0.74 in DM vs 2.76±0.04 in non DM; p=0.04) were significantly lower in DM patients. GFR did not statistically differ between DM and non DM patients (85±28 vs 86±25 ml/min/1.73m², respectively; p=0.96) with 42% of pa-
ients in class I and 58% in class II-III renal dysfunction. In DM patients a significant direct correlation was found between GFR and CPT-CFR (r=0.55, p=0.007), but not between GFR and Dip-CFR. In DM patients with GFR above the median (75 ml/min/1.73m²), CPT-CFR was significantly higher (1.52±0.19) than in DM patients with GFR below the median (1.33±0.20; p=0.00), whereas no differ-
ence was found for Dip-CFR (2.48±0.75 vs 2.30±0.70; p=0.57). Moreover, a weak significant correlation was found between fasting glycemia and CPT-CFR (r=0.34, p=0.016) but not with Dip-CFR.

Conclusion: In DM patients without epicardial coronary stenosis microvascu-
lar function is significantly impaired compared to non DM patients with similar risk factors. However, only endothelial dependent CFR significantly correlates to GFR. These findings support the role of endothelial dysfunction as common pathogenetic mechanism of renal and myocardial dysfunction in DM patients.

P4497
The Impact of ECG Change during Intracoronary Acetylcholine Provocation test on the 12 months Clinical Outcomes in Korean patients

S.W. Rha1, J.Y. Park2, S.K. Ryu2, J.W. Choi2, B.G. Choi1, A. Elnagar1, S.I. Im1, S.W. Kim1, C.U. Choi1, D.J. Oh1, 1Korea University Guro Hospital, Seoul, Korea, Republic of; 2Eulji University, Seoul Eulji Hospital, Seoul, Korea, Republic of

Background: The ischemic electrocardiography (ECG) changes are known to be a predictor of ischemic heart disease. However, whether the ischemic ECG changes occurring during acetylcholine (Ach) provocation test is associated with clinical outcomes is largely unknown. We evaluated the impact of ischemic ECG changes occurring during Ach test on Ach induced coronary artery spasm (CAS) and 12 months clinical outcomes.

Methods: A total 2441 consecutive pts without significant coronary artery disease who underwent the Ach test were enrolled between November 2004 and Octo-
ber 2010. Ischemic ECG changes were defined as ST elevation, ST depression, and deep T wave inversion. The patients were divided two groups according to ischemic ECG changes occurring during Ach test (ischemic ECG changes group: n=88, control group: n=1305).

Results: At baseline characteristics, there were no differences between two groups. At angiographic characteristics, the incidence of basal spasm (43.8% vs 30.7, p=0.010), multivessel (58.4% vs 36.9%, p=0.003) and diffuse (92.1% vs 81.0%, p=0.001) spasm were higher in the pts with ischemic ECG changes. At 12 month clinical outcomes, the incidence of cardiac death (2.2% vs 0%, p=0.001) and myocardial infarction (1.1% vs 0%, p=0.003) were significantly higher in the pts with ischemic ECG changes (table). Multivariate analysis showed that the is-
chemic ECG change was an independent predictor of mortality (odds ratio: 125.3, 95% confidence interval: 3.5-4472, p=0.008) up to 12 months.

Table 1. 12 months clinical outcomes

<table>
<thead>
<tr>
<th>Ischemic ECG change (n=88)</th>
<th>Control (n=1305)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>2 (2.2)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>2 (2.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>PTCa</td>
<td>1 (1.1)</td>
<td>7 (0.5)</td>
</tr>
<tr>
<td>CVA</td>
<td>0 (0.0)</td>
<td>4 (0.3)</td>
</tr>
</tbody>
</table>

Conclusion: In this study, ischemic ECG change occurring during Ach test was associated to 12-month clinical outcomes. Therefore, if the ischemic ECG change was observed during Ach test, intensive antithrombic treatments and close clinical follow up would be needed.

P4498
Association of myocardial bridge and acetylcholine induced coronary artery spasm and 12-months clinical outcomes

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Background: Myocardial bridge is known to be a strong predictor of coronary artery spasm (CAS). However, whether myocardial bridge (MB) is associated with clinical outcomes is largely unknown. We evaluated the impact of MB on CAS induced by acetylcholine (Ach) provocation test and 12 months clinical outcomes.

Methods: A total 2441consecutive patients (pts) without significant coronary
artery disease who underwent the Ach test were enrolled between November 2004 and October 2010. The pts were divided into two groups according to MB (MB group: n=367, control group: n=1027).

Results: At baseline characteristics, the pts with MB had higher incidence of old age (53.2% vs 55.6%, p=0.016), male gender (59.9% vs 46.8%, p=0.0002), and hyperlipidemia (13.6% vs 16.3%, p=0.0408) than the pts in control group. At Ach provocation test, the pts with MB had higher incidence of Ach induced CAS, multivessel and diffuse spasm than the pts in control group (Table 1). Multivariate analysis showed that MB was a predictor of Ach-induced CAS (odds ratio: 2.885, 95% confidence interval: 2.2-3.7, p=0.001). However, At 12 month clinical outcomes, there were no significant difference between two groups (Table 1).

Table 1. 12 months clinical outcomes

<table>
<thead>
<tr>
<th>Case</th>
<th>MB (n=367)</th>
<th>Control (n=1027)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACC</td>
<td>5 (1.4)</td>
<td>8 (0.7)</td>
<td>0.31</td>
</tr>
<tr>
<td>Morality</td>
<td>1 (0.3)</td>
<td>3 (0.2)</td>
<td>0.95</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0 (0.0)</td>
<td>2 (0.1)</td>
<td>0.39</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0.0)</td>
<td>1 (0.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>PTC</td>
<td>2 (0.5)</td>
<td>6 (0.5)</td>
<td>0.93</td>
</tr>
<tr>
<td>CVA</td>
<td>2 (0.5)</td>
<td>2 (0.1)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Conclusion: In this study, MB was associated with Ach induced CAS, and multivessel and diffuse spasm. But MB was not associated with the 12-months clinical outcomes.

CONCLUSION AND OXIDATIVE STRESS: FROM BENCH TO PRACTICE

Exendin-4 postconditioning is not effective in hearts isolated from hypertensive SHR-SP rats with left ventricular hypertrophy

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Purpose: Exendin-4 (ex4) postconditioning has been shown to limit reperfusion injury (RI) in experimental [1] and clinical [2] settings. Left ventricle hypertrophy (LHi) may be associated with increased RI. Few studies have addressed the efficacy of various conditioning treatments for RI in LHi. We studied ex4-ex4 postconditioning in hearts isolated from SHR-SP (hypertensive LHi) rats.

Method: Hearts isolated from WKY (control) and SHR-SP rats (11-15 weeks old) were subjected to 35 min LAD occlusion-2 hrs reperfusion, with ex4 0.3 nM present during the first 15 min in treated hearts. Evans blue/TTC method was used to determine area-at-risk (AAR) and infarct size (% of AAR). Akt phosphorylation (Akt-P) was measured on western blots after 3 min of reperfusion. Arterial blood pressure (BP) was measured in conscious animals by tail cuff method.

Results: ex4 and heart/body weight ratio were increased in SHR-SP compared to WKY rats (169±3 vs 129±4 mmHg, N=8-10; and 3.43±0.05 vs 2.35±0.03, N=15-18; P<0.0001 for both parameters). Infarcts were larger in SHR-SP than in WKY (65±3.3 vs. N=10). Infarct size diminished following ex4-ex4 postconditioning of WKY hearts (to 21.8±6.5; N=6; P<0.05), but not SHR-SP hearts (64.0±4.7; N=7). In WKY hearts, ex4 treat-
Impact of ischemic postconditioning in acute myocardial infarction patients with preconditioning

Background: Both ischemic preconditioning and postconditioning have been found to reduce myocardial damage in acute myocardial infarction (AMI). However, in animal models of ischemia and reperfusion, additive cardioprotective effects by ischemic preconditioning and postconditioning were unexpectedly contradicted. The present study aimed to determine whether postconditioning would provide more powerful cardioprotection in AMI patients with prodromal angina.

Method: The consecutive 82 AMI patients with single vessel occlusion, gained postconditioning (PoC) and pauses (PA) within 7 days of the onset. We evaluated area at risk with BMIPP and 99mTc-tetrofosmin (Tetrofosmin) and 123I-BMIPP (BMIPP) SPECT were performed within 7 days of the onset. We evaluated area at risk with BMIPP and calculated salvage ratio from severity scores of Tetrofosmin.

Results: There were no significant differences in age, time to reperfusion, collateral development, left ventricular ejection fraction, and area at risk among four groups. However, the cumulative CK-MB levels in Pa(+)- groups were significantly smaller than PoC(-)Pa(-) (PoC(+)-Pa(+)): 817±489 IU/l, PoC(-)Pa(+): 912±528 IU/l, PoC(+)-Pa(-): 1327±629 IU/l, PoC(-)-Pa(-): 1327±629 IU/l, p<0.05, respectively. Only in the group of PoC(+)-Pa(+), the salvage ratio was significantly greater than the groups of PoC(-)Pa(-) (PoC(-)-Pa(+)) (63±13%, PoC(-)-Pa(-)) (52±14%, PoC(+)-Pa(-)) (48±13%, p<0.05, respectively). Surprisingly, in the groups of PoC(+), the incidence of serious reperfusion arrhythmia such as ventricular tachycardia remarkably reduced than the groups of PoC(-) (PoC(-)-Pa(+)) (0%, PoC(-)-Pa(-)) (8%, PoC(+)-Pa(-)) (18%, PoC(+)-Pa(-)) (29%, p<0.05, respectively).

Conclusions: We demonstrated that cardioprotective effects of ischemic post-conditioning were significantly and additively enhanced in AMI patients with prodromal angina, opposite to previous experimental studies of animal models.

Discussion: These data suggest that hypertensive LVH may be associated with a loss of efficacy of ex4 preconditioning, as shown earlier for erythropoietin [3] and ischemic [4] preconditioning. Insufficient Akt-mediated signaling might contribute to this impairment.

References:
Effect of sildenafil on mitochondria in rat myocardial infarction model - morphological and property changes utilizing atomic force microscopy

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Objectives: Many studies showed that sildenafil have cardioprotective effects mediated by nitric oxide and ischemic preconditioning. Mitochondria play critical roles in both the life and death of cardiac myocytes. We tested whether sildenafil could make rat hearts resistant to infarction through mitochondrial protection using atomic force microscopy (AFM).

Methods: To prove the cardiac protective effect of sildenafil and investigate the morphologic and property analysis of mitochondria by AFM in the rat myocardium, in-vivo myocardial infarction (MI) model were used. Rat hearts were subjected to 40 min local ischemia by ligation of the left anterior descending (LAD) coronary artery and examined at different times. The isolated mitochondria were analyzed using atomic force microscopy.

Results: Infarct area was significantly reduced in sildenafil-treated rats (7.76±3.98% vs. 20.37±7.02% in sildenafil and control hearts, respectively, \( p < 0.001 \)) as in the previous studies. Thus a relative reduction of 62% in the infarct zone was observed in the sildenafil-treated rats. From the shape parameters of mitochondria in AFM image, it seemed that myocardial infarction caused the mitochondrial swelling (1,495±1,139 nm² in normal vs. 24,150±18,289 nm² in MI, \( p < 0.0001 \)). Whereas sildenafil reduced the mitochondrial area (7,428±3,682 nm² vs. 7,078±1,827 nm² of control, \( p = 0.001 \)) by 69.23% compared to that of MI. In addition, sildenafil-mediated cardioprotection was associated with mitochondrial KATP channel.

Conclusions: Sildenafil could make rat hearts resistant to infarction through mitochondrial protection. Many studies showed that sildenafil have cardioprotective effects mediated by nitric oxide and ischemic preconditioning. Mitochondria play critical roles in both the life and death of cardiac myocytes. We tested whether sildenafil could make rat hearts resistant to infarction through mitochondrial protection using atomic force microscopy (AFM).
Diastolic dysfunction: epidemiology and mechanism

Old tools in new combination: combined stress echocardiography cardiopulmonary exercise testing in early detection of diastolic dysfunction


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Background: Echocardiography is shown to be very important clinical tool for detection of diastolic dysfunction (DD) at rest in patients with hypertensive heart disease. However, simple diagnosis and stratification of patients according to severity and functional impairment in patients with exertional dyspnea and normal baseline values, without cardiopulmonary exercise testing (CPET). Relationship between diastolic function (DF) and CPET during combined stress testing was still not well understood.

Objective: To assess integrated simultaneous evaluation of both echocardiographic variables and parameters of CPET in pts with hypertensive, exertional dyspnea; normal baseline systolic and DF.

Methods: We studied 100 pts (68 male, mean age 51±14 years), with the history of hypertension, exertional dyspnea and normal baseline echo characteristics (including normal baseline systolic and DF). They all underwent CPET with supine ergometry with incremental ramp protocol (15W/min), with breath by breath gas analysis, in combination with simultaneous monitoring during CPET. We assessed systolic and diastolic function at baseline and at maximal exercise. DF was assessed by analyzing transit flow pattern using pulse Doppler and tissue Doppler (TDI) of mitral annulus. Mitral E wave/ Ewave of mitral annulus > 8 was cut off for impaired DF.

Results: All patients had left ventricular ejection fraction >50%, and none of them had exercise induced myocardial ischemia. Worsening of DF was found in 45% pts during combined CPET stress test. Patients with DD were older (p<0.001), and had lower peak VO2 (p=0.001), shorter time to VAT (p=0.008) and shorter total exercise time (p=0.017), and higher VE/VCO2 slope (p=0.001). However multivariate analysis showed that only VE/VCO2 was independent predictor of DD during CPET (p=0.001). RR 1.68; 95%CI: 1.24-2.24. We also found the strong correlation between VE/VCO2 slope and E/e’ (r=0.70; p=0.0001) which can be also used for stratification of pts with DD.

Conclusion: Integrated evaluation of both exercise induced echocardiographic changes and respiratory gas analysis during combined stress CPET stress test shows improved detection and clinical assessment of DD in patients with exertional dyspnea and normal baseline LV function. It adds more information to echo and CPET as a possible tool for the early and accurate detection of DD and allows for an early intervention.

P4511 Anthracycline cardiotoxicity: incidence at present time


Purpose: Chronic Anthracycline cardiotoxicity (AC) characteristically presents within the first year after treatment with a peak of incidence 3 months after the end of Chemotherapy (CHT). Limitation of use of these agents in cancer treatment is related to exercise capacity and pts selection is lower than previously published data due to progression of the underlying cancer disease. Twelve pts (15%) had baseline diastolic dysfunction and 38 pts (47%) developed diastolic dysfunction which was permanent in 29pts (36%). Twenty nine pts (36%) didn’t develop significant diastolic changes.

Conclusions: Chronic AC expressed as asymptomatic diastolic dysfunction is common. However incidence of subclinical systolic dysfunction with current chemotherapy schemes and pts selection is lower than previously published data and it doesn’t carry relevant clinical consequences.

P4512 Relation between diastolic function in rest and during stress and peak exercise capacity among heart transplant recipients

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Purpose: Several studies have shown that diastolic dysfunction impairs exercise capacity despite normal left ventricular ejection fraction (LVEF). This may also be a contributing factor in the limited physical performance of heart transplant recipients (HTX). We studied whether diastolic dysfunction at rest and during exercise is related to exercise capacity and the ability to improve exercise capacity after training intervention.

Methods: 23 stable HTX pts (mean age 50.4±14.8) with normal LVEF underwent maximum bicycle exercise test and semi supine exercise stress echocardiography. 13 patients underwent 8 weeks aerobic interval training and had echocardiography and exercise test repeated. Standard resting echocardiography included pulsed Doppler LV inflow apical 4 chamber (A, E, dec. time) and pulsed TDI (e’ calculated as mean of lateral, septal, anterior and posterior corner of mitral annulus). Acquisitions were repeated at 30% and 60% of maximum workload and during recovery.

Results: VO2peak increased from (mean ±sd): 23.8±7.0 to 28.3±6.4 ml/kg/min (p=0.001) after training. Only few of the patients exhibited diastolic dysfunction at rest, but during stress echocardiography E/e’ increased and deceleration time decreased, unmasking sign of diastolic dysfunction. Diastolic dysfunction at rest and stress or the change in diastolic measures from rest to 60% did not predict workload at VO2peak at baseline or improvement in VO2peak.

Conclusion: In contrast to previous studies of other cardiac patients, we found no correlation between diastolic function in rest and during stress echocardiography and VO2peak or improvement in VO2peak after 8 weeks aerobic interval training in heart transplant patients. Diastolic function may not be a limiting factor for exercise response when chronotropic response is impaired.

P4513 Diastolic dysfunction is associated with reduced exercise capacity in non-obese subjects. Results from a population-based study sample

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Background: Left ventricular (LV) diastolic dysfunction has been reported to be associated with exercise capacity in heart failure and in patients referred for exercise testing. However, this relationship has not been studied extensively in the general population.

Methods: Data of 1,344 subjects (737 women, 607 men) aged 25-85 yrs from the population-based Study of Health in Pomerania (SHIP) in Germany with echocardiographic data on systolic and diastolic LV function and without reduced LV systolic function (LVEF<50%) were included in the analyses. All subjects volunteered symptom-limited cardiopulmonary exercise testing. The association of diastolic dysfunction with exercise capacity as assessed by peak oxygen uptake...
Diastolic dysfunction: epidemiology and mechanism / Heart failure with preserved ejection fraction-echo investigation

P4514
The association between computed tomography-derived three-dimensional pericardial adipose burden, cardiac structural alteration and diastology

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Purpose: Pericardial adipose tissue had been shown to exert their local effect on adjacent cardiac structures. However, data regarding three-dimensional volume measurements of such visceral adipose burden on myocardial diastolic function remained largely unknown.

Methods: We consecutively assessed pericardial fat tissue (PCF) by volume-based three-dimensional measure utilizing computed tomography (Aquarion 3D Workstation, TeraRecon, San Mateo, CA, USA) from 268 subjects after exclusion of decompensated heart failure. Diastolic parameters including left atrial (LA) diameter, early mitral inflow velocity (E), early-to-late inflow ratio (E/A), isovolumetric relaxation time (IVRT), and high frame-rate speckle tracking tissue Doppler imaging (TDI) including lateral mitral annulus systolic (E') and early diastolic (E') velocities were all obtained. Left-sides filling pressure was estimated by E/E' ratio.

Results: Of all 268 subjects (mean age: 53.5 years, 31% female) enrolled, 81 (35.8%) had hypertension and 29 (12.9%) had diabetes with an average PCF (35.8%) had hypertension and 29 (12.9%) had diabetes with an average PCF (ESPV and EDPVR) were markedly shifted leftwards (PV) analysis. In DOCA vs control, baseline cardiac output (6.0±0.5 vs 8.6±0.6 l/min) and heart rate (95±5 vs 84±6 bpm) were different, while LV ejection fraction (68±3 vs 51±3%) was higher (p<0.05). The end-systolic and end-diastolic PV relationships (ESPVR and EDPVR) were markedly shifted leftwards in DOCA vs control (p<0.05).

Conclusion: Increasing pericardial visceral burden was independently associated with impaired diastolic function, leading to left atrial dilation and elevated filling pressures. Our study suggested the possible link between excessive pericardial fat accumulation, altered cardiac geometry and diastolic dysfunction.

P4515
The relationship between left atrial systolic function and left ventricular performance in heart failure with preserved ejection fraction

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Background: Clinical features of heart failure with preserved EF (HFPEF) have not been well characterized. It is reported that peak atrial systolic mitral annular velocity (A') predicts left atrial (LA) systolic function. The aim of the present study was to investigate the relationship between LA systolic function and left ventricular (LV) performance in HFPEF.

Methods: Out of 327 patients who presented to the emergency department because of acute pulmonary congestion during the last 5 years, those with EF > 50% upon admission comprised the HFPEF patients (n=56) enrolled in this study.
Patients with atrial fibrillation or mitral valvular disease were excluded in this study. A control group (Gr-C) consisted of consecutive 30 hypertensive patients with EF of > 50%. We recorded tissue Doppler-derived peak early diastolic and atrial systolic velocities of (m/s) respectively in the chronic stage. Other echo parameters (LA diameter (LAD) and LV diastolic function (LVDd) and E/E') were measured at the same time. The HFPEF patients were divided into the good LA function group (Gr-G) (A' > 6cm/s, n=30) and the poor LA function group (Gr-P) (A' < 6cm/s, n=21) depending on the score of A'.

Results: E/E' was correlated with A' (y=10.92-0.24x (r=0.4609, p=0.0069)) in the Gr-G patients. A and E were the lowest and E/E', LAD and LVdOd were the highest in Gr-P (table).

LA systolic function and LV performance

<table>
<thead>
<tr>
<th></th>
<th>A' (cm/s)</th>
<th>E (cm/s)</th>
<th>E/E'</th>
<th>LAD (mm)</th>
<th>LVDd (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr-C</td>
<td>8.5 ±1.6</td>
<td>6.4±1.7</td>
<td>10.9±2.0</td>
<td>38.1±5.3</td>
<td>48.9±4.7</td>
</tr>
<tr>
<td>Gr-G</td>
<td>7.0±1.9</td>
<td>5.0±1.4</td>
<td>12.2±3.5</td>
<td>41.5±4.9</td>
<td>50.5±6.4</td>
</tr>
<tr>
<td>Gr-P</td>
<td>4.2±0.8</td>
<td>3.7±0.8</td>
<td>17.8±4.3</td>
<td>45.9±2.3</td>
<td>55±6.4</td>
</tr>
</tbody>
</table>

*p<0.05 vs Gr-C and Gr-G, *p<0.05 vs Gr-C.

Conclusions: The progression of LA systolic dysfunction was associated with the impairment of LV diastolic function and may play an important role in the pathogenesis of HFPEF.

Radial dyssynchrony was detected in 12% of patients at rest which increased to 29% patients on exercise. SDradial on exercise correlated with Radial strain on exercise (r=-0.246, p=0.022).

EF (57.3±7.3% vs 60.4±9.7%), we observed larger left atrial diameter (49.7±6.9 mm vs 44.7±6.4 mm, p=0.050) and area (28.8±6.2 cm² vs 24.5±5.1 cm², p=0.044) in patients with endpoint vs. no endpoint. Patients with clinical endpoint showed more anteroseptal and posterior wall myocardial ultrasound reflectivity (-12.3±6.0 dB vs. -22.7±8.1 dB, p=0.0024 and -14.9±6.1 uls. vs. -21.1±8.0 dB, p=0.031) as compared with event-free patients.

Conclusion: Our data support the hypothesis that calibrated CIB, a surrogate for myocardial fibrosis, identifies HFPEF patients at risk of death or HF hospitalization.

Left but not right ventricular dyastolic dysfunction deteriorates during follow up in patients with systemic sclerosis

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Systemic sclerosis (SSc) is characterized by vascular changes and fibrosis of the skin and internal organs. There are limited data on left (LV) and right ventricular (RV) diastolic function in SSc patients particularly in follow up and their relations to parameters of collagen metabolism.

To analyze LV and RV diastolic function during follow up in patients with SSc and its relation to serum TIMP 1 (tissue inhibitor of metalloproteinase 1) levels, a biomarker of matrix remodeling.

Methods: We prospectively studied 69 consecutive pts (64F, 5M mean age 55.5±13.8 yrs) with SSc (mean SSc duration 9±12.4 yrs) at baseline and after at least 1 year of follow up (3±1.1 yrs). TTE (Philips IE 33) for assessment of LV and RV diastolic function was performed. We also measured serum TIMP-1 (Human TIMP-1 immunoassay R&D Systems) levels. At fu we observed significant deterioration of Doppler parameters of LV but no RV diastolic function. Mean TIMP-1 serum concentration was higher at SSc follow up patients (204.6±167.1 ng/ml, p=0.0001). In SSc fu group TIMP-1 correlated positively to mitral lateral and septal E/E' (r=0.4, p=0.0019 and r=0.32, p=0.01), and negatively to early diastolic lateral velocity E' (-0.46, p=0.0003) and early diastolic septal velocity E' (-0.38, p=0.003).

LV and RV diastolic function in SSc pts

Parameter | SSc (n=69) | SSc follow up (n=69) | p
---|---|---|---
Mitral E/A | 1.09±0.1 | 0.92±0.3 | 0.02
DT (ms) | 175.6±36.6 | 198.6±36.6 | 0.001
PVS F (cm/s) | 59.4±10.4 | 63.6±16.6 | 0.03
S/G | 1.21±0.28 | 1.38±0.23 | 0.06
PVF A (cm/s) | 29.5±7.4 | 33.3±8.1 | 0.0063
Mitrual E' lateral | 7.5±3.1 | 6.9±2.5 | NS
Mitrual E' septal | 9.4±7.3 | 9.5±6.3 | NS
Tricuspid E' lateral | 1.05±0.2 | 1.02±0.2 | NS
Tricuspid E' septal | 4.7±1.35 | 4.8±1.54 | NS

DT, deceleration time; PVS F, peak systolic inflow velocity; PVF A, peak velocity of regurgitated atrial flow.

Conclusions: LV but not RV myocardial relaxation deteriorate during follow up. TIMP-1 is significantly correlated with echocardiographic parameters suggesting a potential link for LV diastolic dysfunction and matrix remodeling in patients with SSc.
Left ventricular torsion during exercise in patients with and without increase in left ventricular filling pressures

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Left ventricular torsion (Tors) is increased in patients (pts) with diastolic dysfunction but little is known about the effect of exercise (Ex) on Tors in them. We aimed to assess Tors during Ex in pts with and without increase in left ventricular filling pressures.

Methods: We studied 132 consecutive pts with normal LV ejection fraction (LVEF >50%), and normal Ex echocardiography. Speckle imaging was performed in rest (R) and at peak (Pk). Tors was defined as maximal apical rotation – basal rotation (°) / LV length (cm). Confident tracking assessment was achieved in 107 pts (81%). Volumetric UVEF and the ratio of early to transmural flow were measured at the left ventricular end-diastolic pressure by the mitral annulus waves (E/A) / E at R and at Pk were also measured. Twenty-six pts had E/e’ ratio ≥ 15 (G-HHe) and 81 pts <15 (G-NHe).

Results: G-HHe pts were older (67±9 vs. 56±14, p=0.001) and achieved less METs (8.8±3.7 vs. 7.1±4.0, p=0.02). A history of coronary artery disease was equally frequent (8% in G-HHe and 21% in G-NHe, p=0.15). LVEF at R was higher in G-HHe (70±9 vs. 66±8, p=0.04) whereas it was similar at Pk (74±9 vs. 70±8, p=0.08). E/e’ values at R were 14.5±5.3 in G-HHe and 10.5±2.6 in G-NHe (p=0.001), whereas at Pk it was 18.9±11.1 and 9.8±2.9, respectively (p<0.001). Rotation parameters were similar between groups except for apical rotation which was higher at R and Pk in G-HHe.

Conclusion: These results suggest that exercise may be associated with increased Tors.

References:

Moving toward an ejection fraction paradox: the ratio between left ventricular and left atrial volume

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Background: We hypothesize that the ratio between left ventricular end-diastolic volume (LVEDV) and end-systolic left ventricular area (LA-LVSA) ratio may better estimate the severity of the HF, being a sum of a long term history of systodiasis dysfunction.

Methods: Out-patients attending a community HF service between 2008 and 2010 were enrolled. HF was defined as the presence of relevant symptoms and signs and objective evidence of cardiac dysfunction: either a left ventricular ejection fraction (LVEF) <45%, or the combination of both left atrial (LA) dilatation (>4cm) and raised amino-terminal pro-brain natriuretic peptide (NTproBNP) >400 pg/ml.

Results: Amongst the 693 patients included, median age was 73 years, 33% were women and HF was confirmed in 568. LA-LVSA ratio (SD) in patients with no HF (n=125) was 2.1 (0.8), the mean LA-LVSA ratio for each quartile in patients with HF was 3.8 (1.2) vs. 2.3 (0.9) vs. 1.6 (0.6) vs. 1.0 (0.2). Comparing patients with HF in the lowest and highest quartile of LV-LA ratio, those in the highest quartile were older, had more signs of HF, were more likely to have atrial fibrillation and to be treated with diuretics, had higher pulmonary pressures but had more negative values (better function) for global longitudinal strain (GLS, -12.3 (4.3) % vs. -7.4 (3.3) %, p=0.001) and higher LVEF (54 (12) % vs. 32 (9) %, p=0.001). LVC diameter was larger (22.3 (5.1) vs. 17.6 (3.3) mm, p=0.001) and NTproBNP plasma levels were more elevated (1968 (12) IQR 3727) vs. 1044 (401-2241 ng/l, p=0.001). During 567 (IQR: 413 – 736) days of follow up there were 158 events (78 patients were admitted to hospital with heart failure and 80 died due to CV causes). The Kaplan-Meier curves show that patients in the highest quartiles of LV- LA ratio have the highest risk of adverse outcome and this risk decreases accordingly with the increasing LA-LVSA ratio. In a multivariable Cox regression model, including NTproBNP, LA-LVSA ratio, but not LVEF, was an independent predictor of worse outcome.

Conclusions: In patients with chronic HF with or without a reduced LVEF, the LV- LA ratio identifies patients with higher NTproBNP and worse outcome who paradoxically have higher LVEF.

Deceleration time of early diastolic velocity by tissue Doppler velocity image: a novel index of left ventricular end-diastolic pressure

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Purpose: This study aimed to examine the diagnostic utility of the deceleration time (DT) of early diastolic velocity of mitral annulus by tissue Doppler imaging, a method for the assessment of left ventricular end-diastolic pressure.

Methods: Simultaneous left ventricular catheterization and Doppler echocardiography were performed to compare the left ventricular end-diastolic pressure (LVEDP) and DT in 57 patients who were scheduled for diagnostic coronary angiography. They were admitted to our hospital for the assessment of heart disease including cardiomyopathy (n=26) and coronary artery disease (n=31). We excluded the patients with atrial fibrillation and mitral valvular disease and who underwent mitral valvulav surgery. Color-coded tissue Doppler images were acquired at apical 4 chamber view, and DT of early diastolic velocity measured at mitral annulus were assessed. DT was also evaluated in 15 healthy subjects.

Results: DT is successfully measured in all subjects. DT in the patients with elevated LVEDP (>18mmHg) (69±12ms, n=14) was significantly shorter than those with LVEDP<18mmHg (94±18ms, n=43) and healthy subjects (100±11ms). DT is inversely proportional to LVEDP (r=0.7, p<0.0001). With a cut-off value of DT of 80 ms, which was determined by receiver operating characteristic curve, the

In conclusion, characteristics of pts with high E/e’ values include old age, low functional capacity, and increased apical rotation at R and at Pk.

References:

ventricular-arterial coupling and arterial stiffness in hypertensive subjects with diastolic heart failure

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Objective: To compare ventricular-arterial coupling (Ea/IvLve) and arterial stiffness indices in hypertensive subjects with and without heart failure with preserved ejection fraction (HFPEF).

Methods: The study included 66 hypertensive patients with stable NYHA class II-III HFPEF (26 male, age 71.8±8.7 years, clinic BP 130±190/80±80 mmHg, EF 61±8%,). HFPEF was confirmed by NTproBNP >100 pg/ml (Me 873, min 112 - max 3000 pg/ml). Control group included 20 hypertensive patients (male 5, female 15, age 70±7.9 years, clinic BP 136±20/87±12 mmHg) without symptoms of HF and NTproBNP ≤ 100 pg/ml (Me 30, 18-70 pg/ml). All patients underwent central pulse wave analysis (PWA) and wave velocity measurement (PWV) (Sphygmocor, AtCor, Australia) and echocardiography (Vivid 7, GE). Ventricular-arterial coupling index was calculated as Ea/IvLve where EaI=End Systolic Pressure (ESP)/Stroke Volume, IvLve=ESP/End Systolic Volume. Results are presented as Me±SD. Spearman correlation analysis was performed, p<0.05 was considered significant.

Results: Diastolic function indices in patients with HFPEF were IVRT 117.7±40.5 msec, E/A 1.0±0.8, Ee 8.6±3.3, DT 208±77.8 ms, in control group 110.7±42.5 msec; 0.7±0.1, 6.7±1.7; and 173.8±49.3 msec, respectively. In control group all patients had symptomatic type 1 diastolic dysfunction. Age-adjusted PWA revealed no differences between patients with HFPEF and control subjects: central BP 126±197/9±12 vs 121±18/81±8 mmHg, pulse pressure (PP) augmentation index=HR75 beats/min 27.4±9.5 vs 25.0±8.9, PWV 121±3.7 vs 10.4±2.4 m/s, respectively. Central PP was significantly higher in HFPEF than in control subjects (48±16 vs 39±14 mmHg, P=0.045). PWV>12 m/s was observed more often in HFPEF (41% vs 15%, p<0.05). Ea/IvLve was similar (0.64±0.2 vs 0.62±1.5, respectively). Ea/IvLve<0.6 was found in 37.8% in subjects with HFPEF and in 30% in control group. Significant correlation was found in patients with HFPEF between E/A and PWV (r=-0.28, p=0.04) and PWV and NTproBNP (r=0.51, p=0.02).

Conclusion: The results obtained suggest similar rates of ventricular-arterial uncoupling in hypertensive subjects with HFPEF and asymptomatic diastolic dysfunction. HFPEF is associated with increased arterial stiffness.
Impact of gender difference on the relation between arterial stiffness and left ventricular diastolic function in healthy subjects

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Background: Diastolic heart failure has been reported to occur more often in elderly women rather than elderly men. Several studies have reported a relation between arterial stiffness and left ventricular (LV) diastolic function. Recently, it was reported that this relation was stronger in women than in men among individuals with cardiovascular risk factors. However, the impact of gender difference on this relation is still poorly understood.

Methods: Study subjects were selected from 447 who had echocardiography and examination of arterial stiffness. Among them, 95 men (mean age, 47.1±11 years) and 72 women (mean age, 47.6±10 years) without atherosclerosis risk factors (hypertension, dyslipidemia, diabetic mellitus) were analyzed. We measured brachial ankle pulse wave velocity (baPWV), carotid augmentation index (AIx) and radial AIx as arterial stiffness parameters immediately after the echocardiographic examination.

Results: Peak early diastolic mitral annular velocity (e') was significantly correlated with baPWV (Men: r = -0.42, p < 0.01; Women: r = -0.54, p < 0.01), carotid AIx (Men: r = 0.26, p = 0.01; Women: r = 0.57, p < 0.01) and radial AIx (Men: r = -0.35, p < 0.01; Women: r = -0.36, p < 0.01). E/e' had a significant correlation with each arterial stiffness parameter in women, but not in men. Multivariate regression analysis revealed carotid AIx (β = 0.26, p = 0.02) was a significant independent predictor of e' in women, but not in men.

Conclusion: Our results suggested that LV diastolic function was more affected by arterial stiffness in women than in men among healthy subjects. This might partially account for a higher incidence of diastolic heart failure in women than men.

Increased prevalence of diastolic heart failure can be identified by impaired global longitudinal strain in patients with rheumatoid arthritis

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Background: Risk of heart failure is increased in patients with rheumatoid arthritis (RA) and is more likely to occur in RA patients with a preserved ejection fraction. Until now little is known about the prevalence of diastolic heart failure (HFNEF) in RA patients. To determine the clinical impact of HFNEF, we therefore examined RA patients with diastolic heart failure measurement using measurement of NT-proBNP level and echocardiography, including strain imaging.

Methods: In this prospective cross-sectional observational study we examined 155 patients (68% female, mean age 60±13 years, 56% hypertension, median BMI 28 kg/m2) with RA according to the current ACR/EULAR criteria in our outpatient clinic for rheumatic diseases. Echocardiography including strain imaging and blood sampling for NT-proBNP were done. HFNEF was diagnosed if (1) symptoms and (2) E/e’-ratio > 15 or (2) NT-proBNP > 220 pg/ml with (3) E/e’-ratio > 8 or (3) atrial fibrillation existed.

Results: There was a surprising high rate of HFNEF (21%) in our RA cohort. The systolic LVEF was reduced only in 4% of patients. LV mass index was increased in 4% of patients and 18% of patients with HFNEF, mostly due to concentric hypertrophy. In the strain imaging we found a significant reduction in the global longitudinal strain in patients with HFNEF with a threshold of -18%.

Logistic regression analysis of HFNEF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate OR (95% CI)</th>
<th>P</th>
<th>Multivariate OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global longitudinal strain ≤ -18%</td>
<td>7.9 (3.1-20.8)</td>
<td>&lt;0.001</td>
<td>14.6 (3.5-61.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age &gt; 65 years</td>
<td>19.0 (6.7-58.8)</td>
<td>&lt;0.001</td>
<td>21.6 (6.0-70.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>6.0 (2.0-19.3)</td>
<td>0.005</td>
<td>21.6 (3.0-140.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>RA activity (DAS28 &lt; 2.6)</td>
<td>4.0 (1.7-10.2)</td>
<td>0.002</td>
<td>7.3 (2.0-24.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>5.9 (2.3-18.8)</td>
<td>&lt;0.001</td>
<td>1.0 (0.3-3.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td>3.2 (1.9-9.4)</td>
<td>0.037</td>
<td>1.0 (0.3-3.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Concentric LV hypertrophy</td>
<td>4.1 (1.7-9.8)</td>
<td>0.002</td>
<td>1.0 (0.3-3.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>History of CAD</td>
<td>7.5 (2.1-23.7)</td>
<td>0.002</td>
<td>1.0 (0.3-3.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Duration of RA &gt; 15 years</td>
<td>3.32 (1.46-7.72)</td>
<td>0.005</td>
<td>1.0 (0.3-3.7)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Conclusion: This finding in addition to the conventional echocardiographic measurements in HFNEF suggests the role of fibrotic endocardial changes in diastolic heart failure in RA. Markers of RA activity (DAS28) were significant risk factors beyond classical risk factors like age, female gender, hypertension and diabetes mellitus type 2.


**DIASTOLIC DYSFUNCTION AND TREATMENT**

**P4529**

Differing relations of the clinical responder rate to the left ventricular reverse remodelling and changes in left ventricular filling pattern in patients receiving cardiac resynchronization therapy

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**Background:** Clinical responder rate (CRr) and left ventricular (LV) reverse remodelling (RR) are regarded valuable markers of long-term favourable effects of cardiac resynchronization therapy (CRT). Besides the aforementioned parameters, the improvement of LV diastolic function (LDFD) might also be another valuable predictor of the long-term response to CRT.

**Aim:** To assess the relation of the CRr to the LVRR and to the improvement of LVDF evaluated in improving LV diastolic filling pattern (LVIFP) in pts receiving CRT. To investigate the survival of pts according to RR and LVIFP.

**Patients and methods:** 139 pts with CRTp (51%) or CRTd (49%) followed prospectively for 38.6±23.8 months. Age 64.1±10.6 years, male 81.2%, ischemic 37.4%, diabetes mellitus 35.4%, atrial fibrillation 23.6%, NYHA 2.8±0.8, blood pressure 116.4±21.6/72±6.2/12±8.8 mmHg. LV ejection fraction (LVEF) ≤ 35%

- **Cardiac function parameters:** 20 cases, 62.5% mean LV end diastolic pressure (LVEDP) estimation (based on ASE recommendation, Nagaeu et al 2009) and diastolic dysfunction stages (DD) were recorded. Data was analyzed using paired t test.

**Results:** At one year, 3% had normal LVEF, 13% had moderately depressed LVEF, 58% had severely depressed LVEF and 26% had not surviving pts according to RR and iLVFP were nearly the same: in surviving pts LVRR was found between RR and CRr. iLVFP was associated with 100% of CRr in lack of follow-up.

- **Conclusion:** Improvement of LVDF in patients receiving CRT might be an additional valuable predictor of CRT long-term response.

**P4530**

Creatine Phosphate Sodium combining with fructose diphosphate for injection on severe diastolic heart failure

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chengu second people’s hospital, chengdu, China, People’s Republic of

**Background:** High-energy phosphate stores, especially creatine phosphate (CP) and product of ATP, are reduced and their consumption increased in diastolic heart failure (DHF). We hypothesized that improvement of abnormality of energy metabolism with Creatine Phosphate Sodium (CrP) combining with fructose diphosphate (FDP) for injection may be significant since diastolic heart failure especially on moderate and severe diastolic dysfunction are associated with increased mortality and lack of effective treatment.

**Methods:** Randomized double-blind self-cross controlled studies were performed with CP (5g/d), FDP (1g/d) or CP (1g/d) + FDP (5g/d) in 30 patients with diastolic heart failure (22 male and 8 female) and 30 cases of systolic heart failure (21 male and 9 female) and 30 cases of systolic heart failure (21 male and 9 female) received CP (1g/d) + FDP (5g/d) for two weeks and then CP (1g/d) + FDP (5g/d) for one year based on routine treatment with other pharmacologic agents have shown improvement of abnormality of energy metabolism with Creatine Phosphate Sodium (CrP) combining with fructose diphosphate (FDP) for injection may be significant since diastolic heart failure.

- **Conclusions:** Improvement of exercise tolerance and quality of life, and decrease of rehospitalization with CrP therapy combining with FDP may be more apparently than CrP or FDP in severe diastolic heart failure.

**P4531**

Diastolic function improves after resolution of takotsubo cardiomyopathy

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**Background:** Takotsubo cardiomyopathy (TSC) is a condition of reversible left ventricular (LV) systolic dysfunction. However, the diastolic functional (DF) manifestations of TSC have not been widely investigated. We performed retrospective analysis of DF in patients (pts) with TSC during acute and recovery phase.

**Methods:** We studied 27 pts (64±11 yrs, F24) diagnosed with TSC. All pts had echocardiogram in acute phase and at median 3 months follow up. Standard sys- tolic and diastolic function variables including tissue Doppler of mitral annuli (E’), LV end diastolic pressure (LVEDP) estimation (based on ASE recommendation, Nagaeu et al 2009) and diastolic dysfunction stages (DD) were recorded. Data was analyzed using paired t test.

**Results:** During acute phase, 3% (19%) had normal LVEF compared to 10 (63%) at recovery (p<0.001). During acute phase 6 (31%) had elevated LVEDP while none had elevated LVEDP at recovery (p=0.03). Recovery was associated with significant improvement in systolic and diastolic parameters including EF, E/E’, ratio in LVEF ≥2.8 in (Table 2) improvement in E was linearly related to the improvement in EF (ΔE= 0.1*ΔEF + 1.1, n=0, p=0.02).

**Conclusion:** TSC is associated with acute impairment of diastolic function, which improves during recovery. DF recovery parallels systolic recovery in TSC patients.

**P4532**

A low glycemic and insulimcin diet improves diastolic cardiac function and metabolic syndrome more than the traditional low-fat diet in overweight patients with type 2 diabetes

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**Purpose:** Diastolic dysfunction/heart failure in the metabolic syndrome and type 2 diabetes is an epidemic without evidence-based treatment strategies. While recent pharmacologic agents have shown improved cardiac function associated with improved glycemic control and insulin sensitivity, the studies on dietary interven- tions are scarce in spite of the fact that diet may counteract the metabolic syn- drome. Low-carbohydrate nutrition improves postprandial glucose control and in- sulin resistance more than the standard low-fat diet. We tested the hypothesis, that a low-carbohydrate diet improves cardiac function in overweight-obese pa- tients with type 2 diabetes more than the traditional recommended low-fat diet.

**Methods:** Two age and sex matched groups of 16, 10 low-carbohydrate without overt heart disease (52±7 years, body mass index 34±6 kg/m²) were studied in a parallel and partial cross-over design over a 3-week rehabilitation program with either 30 cases of low-fat diet-low fat diet. The group on low-fat diet (carbohydrate 55%, fat 25% and protein 20%) had subsequent 2 weeks on low-carbohydrate diet (25%, 45% and 30%, respectively). Cardiac function was assessed by myocardial veloc- ity during systole and early diastole (E’) using Doppler tissue imaging. Metabolic control was assessed before and 2 h after a standardized breakfast (400 kcal) with low-fat composition at baseline and with low-carbohydrate composition at the final test of low-carbohydrate diet. Both groups had supervised aerobic training 2 hours a day.

**Results:** In the parallel groups, both diets induced similar significant reductions of waist, glycosylated hemoglobin and total cholesterol. Low-carbohydrate diet consid- erably improved insulin resistance, triglycerides, systolic and diastolic blood pressure and diastolic cardiac function (E’=95.1±1.0 to 10.4±1.5 cm/s; p<0.003). None of these variables changed on low-fat diet (E=10.9±1.7 to 10.6±1.5 cm/s), but all of them improved significantly after subsequent low-carbohydrate diet (E=10.6±1.5 to 11.5±1.4 cm/s; p=0.016). Intact proinsulin was unchanged with low-fat diet but decreased with subsequent low-carbohydrate diet, lasting and pp (p=0.032 and 0.004).

**Comparison of echocardiographic variable**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Acute Phase</th>
<th>Recovery Phase</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF %</td>
<td>45±16</td>
<td>60±16.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak E velocity cm/sec</td>
<td>66±15</td>
<td>76±16</td>
<td>0.03</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.9±0.33</td>
<td>1.1±0.53</td>
<td>0.03</td>
</tr>
<tr>
<td>Peak A velocity cm/sec</td>
<td>6.3±2.6</td>
<td>3.7±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E’ (cm/sec)</td>
<td>3.7±1.1</td>
<td>3.7±1.1</td>
<td>0.04</td>
</tr>
<tr>
<td>LV end diastolic diameter (LVEDD):74.2±8.8mm</td>
<td>60±16.6</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>LV end diastolic pressure (LVEDP): estimation (based on ASE recommendation, Nagaeu et al 2009) and diastolic dysfunction stages (DD) were recorded. Data was analyzed using paired t test. LA area cm²</td>
<td>16±3.3</td>
<td>16±3.4</td>
<td>0.01</td>
</tr>
<tr>
<td>atrial lobe bpm</td>
<td>74±15</td>
<td>67±16</td>
<td>0.08</td>
</tr>
</tbody>
</table>
| Normal DF stage n (%): at 6 months 36.8%, at 12 months 40.4%. iLVFP (deceleration width:159.9±22.3ml/min/1.73QRS, width:159.9±32.4ms, left bundle branch block): 89.4%. Treatment: beta-blockers 96%, ACE/ARBs 85%, aldosterone antagonists:71%, direct vasodilators:72%, furosemide:89%, digoxin:33%.

**Table** Improvement in E’ was linearly related to the improvement in EF (ΔE= 0.1*ΔEF + 1.1, n=0, p=0.02).
Conclusions: These data indicate, that a low-glycaemic/high-protein but not a low-fat/high-carbohydrate nutrition modulates diastolic dysfunction in overweight diabetics, improves insulin resistance and may prevent or delay the onset of diabetic cardiomyopathy and the metabolic syndrome.

Adaptive servo ventilation improves long-term prognosis in heart failure patients with preserved left ventricular ejection fraction and sleep disordered breathing

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Background: Effective pharmacotherapy for heart failure (HF) with preserved left ventricular ejection fraction (LVEF) is still unclear. Sleep disordered breathing (SDB) may cause cardiac diastolic dysfunction. A high prevalence of SDB has been documented in HF patients with preserved LVEF. Adaptive servo ventilation (ASV) improves SDB including Cheyne-Stokes respiration. However, it still remains unclear whether ASV improves cardiac function and long-term prognosis of HF patients with preserved LVEF and SDB.

Methods: Twenty five HF patients with preserved LVEF (defined as LVEF of >45%) and moderate-severe SDB (defined as apnea hypopnea index >15 h−1) were enrolled. Study subjects (apnea hypopnea index 39.3±15.2) were divided into two groups: 10 patients treated with conventional medications for HF and ASV (ASV group) and 15 patients treated with conventional medications alone (Non-ASV group). BNP, LVEF, and right ventricular systolic pressure (RVPs) were determined before and 6 months after treatments. Patients were followed to register cardiac events after discharge (average follow up period 728 days).

Results: Although, LVEF did not improve in both groups, BNP and RVPs significantly reduced in ASV group (BNP: 285.8±101.3 to 161.8±62.1 pg/ml, RVPs: 40.5±16.3 to 32.1±8.1 mmHg, P < 0.05, respectively), but not in Non-ASV group. Eight events (death 5, re-hospitalization 3) occurred in this follow up period. Im- portantly, event free rate was significantly higher in ASV group than in Non-ASV group (90.0% vs. 53.3%, logrank P = 0.01).

Conclusions: ASV decreased cardiac overload and improved long-term prognosis in HF patients with preserved LVEF and SDB. ASV might be a promising useful tool for HF patients with preserved LVEF and SDB.

Serum cystatin C as a biomarker of cardiac diastolic dysfunction in patients with cardiac disease and preserved ejection fraction

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Background: Systolic and diastolic functions are independently correlated with cardiac mortality. Worsening renal function also increases mortality and hospitalization known as cardio-renal syndrome. Cystatin C (CysC) is a novel endogenous marker of kidney function. Recently, higher CysC concentrations were demonstrated to be associated with diastolic dysfunction in coronary artery disease without heart failure and chronic systolic heart failure. But it is not clear whether serum CysC is associated with diastolic dysfunction in patients with cardiac disease and with preserved ejection fraction.

Methods: We measured serum CysC, Creatinine and BNP in 124 consecutive patients with cardiac disease. The patients underwent transthoracic echocardiography at rest on the same day. eGFR was determined by the MDRD formula for Japanese. Echocardiographic values were obtained by standard 2-dimensional approach in the parasternal long axis view and apical 4- and 2-chamber views. Trans Mitral Flow (TMF) patterns were categorized into two groups by their E/A ratio, mitral E velocity deceleration time and flow patterns of pulmonary veins.

Results: 124 patients were classified into 5 disease groups according to their cardiac disease. There were no significant differences in serum CysC among 5 disease groups (P = NS). Serum CysC and eGFR showed a significant negative correlation (r = -0.70, P < 0.001), and serum CysC and BNP showed a significant positive correlation (r = 0.49, P < 0.05). In univariate analysis, Cardiac echo parameters (LVEF, LVIDd, LVIDs, E/A, E/E’, LAD, and TMF patterns) were significantly associated with serum CysC (p < 0.01). Multivariate linear regression analysis demonstrated TMF patterns were independent determinants of serum CysC (β = 0.286, P < 0.01). Furthermore, sub-analysis based on patients with preserved ejection fraction (LVEF ≥ 50%) and without renal dysfunction (eGFR ≥ 60 ml/min/1.73 m²), in univariate linear regression analysis, LAD, E/A, E/E’ and TMF patterns, surrogates of cardiac diastolic function, were significantly associated with serum CysC. And multivariate linear regression analysis demonstrated that LAD and TMF patterns were independent determinants of serum CysC (LAD: β = -0.362, P < 0.01; TMF patterns: β = -0.328, P < 0.05).

Conclusions: Serum CysC is associated with diastolic dysfunction in patients with various cardiac diseases and preserved ejection fraction and without renal dysfunction. Our study also suggests that serum CysC become a surrogate biomarker of cardiac diastolic dysfunction in patients with various cardiac diseases and preserved ejection fraction.

Serum vitamin D and CRP levels are independently associated with diastolic dysfunction

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Objective: We hypothesized that serum vitamin D (25(OH)D) levels would be inversely associated with inflammation and with diastolic dysfunction. We therefore investigated the link between serum vitamin D levels and diastolic dysfunction (i.e. diastrometric parameters). We aimed to elucidate whether low vitamin D levels are predictive for diastolic dysfunction.

Methods: The study included 281 patients who were referred for coronary angiography. We measured in all patients 25(OH)D serum levels, C-reactive protein (CRP) and fibrinogen and performed standardized LV echocardiograms. Echocardiographic data were used for classification of systolic and diastolic dysfunction.

Results: 25(OH)D deficiency (<30 ng/ml) was common among our study population (278,8%). Patients with severe diastolic dysfunction had a lower vitamin D levels (14.7±7.9 mg/l, p<0.01), higher CRP levels (p<0.01), higher prevalence of hypertension (p<0.001), diabetes (p<0.01) and higher left ventricular mass index (LVMI) (p<0.01). In multivariate analysis, decreased vitamin D (β = -0.154, p<0.012) and elevated CRP (β = 0.124, p = 0.035) was associated with e’/e ratio after adjustment for potential confounders.

Conclusions: Serum levels of 25(OH)D are significantly associated with LV diastolic dysfunction suggesting that vitamin D supplementation is a promising approach in the prevention of diastolic dysfunction.

Dissecting the mechanisms of left ventricular diastolic dysfunction and inflammation in continuous ambulatory peritoneal dialysis patients

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Background: To investigate the relationship between the amount and anatomic location of adipose tissue depots, inflammation, and left ventricular (LV) diastolic dysfunction in continuous ambulatory peritoneal dialysis (CAPD) patients. LV diastolic dysfunction was diagnosed if the mitral inflow E/A ratio was <1, deceleration time was >220 cm/s, or mitral inflow TDI e’ < -8. CAPD patients with LV diastolic dysfunction served as the control group. Serum adipokine, factors (TNF-α and interleukin-6 (IL-6) were measured, and the location and amount of adipose tissue were assessed by computerized tomography (CT) at the level of the fourth lumbar vertebra.

Results: Subjects with LV diastolic dysfunction had higher levels of the pro-inflammatory cytokines and more visceral and peritoneal fat (all p<0.001) than control subjects. A significant correlation was found between visceral adipose tissue and pro-inflammatory cytokines (r=0.70, P<0.001). Multivariate regression
analysis found that the relationship between visceral adipose tissue and LV diastolic dysfunction became insignificant when either TNF-α or IL-6 were introduced into the model, although TNF-α and IL-6 were both significantly associated with LV diastolic dysfunction even after adjusting for visceral fat (OR=1.51; 95% CI=1.09-2.02; P=0.033 and OR=1.62; 95% CI=1.09-1.82; P=0.031, respectively).

Figure 1. Inflammation and LV DO

Conclusions: Larger amounts of adipose tissue were associated with higher serum pro-inflammatory levels in CAPD patients, which could contribute to the development of LV diastolic dysfunction. Modulating inflammatory reactions in CAPD patients could prove to be a novel therapeutic approach for managing LV diastolic dysfunction.

P4538
Expression of connective tissue growth factor in diabetic heart failure patients and canine models
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Background: Diabetic heart failure (DHF) is characterized by myocardial interstitial fibrosis and left ventricular hypertrophy. Connective tissue growth factor (CTGF) is an emerging marker for tissue fibrosis. The study investigated the association between CTGF and DHF from animal model to clinical indices.

Methods: A total of 120 patients with a diagnosis of DHF confirmed by echocardiography and 60 matched controls were recruited. Soluble plasma levels of CTGF were measured in all subjects and the associations with diastolic function parameters were calculated. Canine model of DHF was induced by aortic banding. Left ventricular (LV) pressures, LV volumes, and transmural Doppler were obtained before and after pressure loading (at baseline and after 6 months). Myocardium tissues were collected, and western blotting was used to detect the protein expression of CTGF for each dog. The correlation for CTGF and the severity of diastolic dysfunction was then calculated.

Results: Patients with DHF presented significantly higher CTGF levels than the controls. Significant correlations (all P < 0.05) were found for CTGF and E/e' (r = 0.55), E/A (r = 0.5) in advanced DHF patients (E/e' > 15). After 24 weeks in canine models, the protein expression of CTGF from LV myocardial tissue was significantly increased (p = 0.01) compared with the controls (sham dogs). Moreover, the expression of CTGF paralleled the severity of LV diastolic dysfunction parameters and hemodynamic changes.

Conclusions: Both Plasma and myocardium CTGF levels had significant correlations to the severity of DHF. Our study offered the evidence to apply novel therapies for DHF patients aim to down-regulate the overexpression of CTGF.

P4539
Resveratrol, a SIRT1 activator, prevents cardiomyopathy in dystrophin-deficient mice by down-regulation of p300
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Background and purpose: Heart failure is a main cause of death in patients with Duchenne muscular dystrophy (DMD), a disorder caused by defective gene for dystrophin. However, there is no effective therapy for prevention of heart failure in DMD. The aim of this study was to examine whether activation of SIRT1, an NAD+-dependent histone/protein deacetylase, by use of resveratrol prevents cardiomyopathy due to dystrophin deficiency.

Methods and results: We used dystrophin-deficient mice (mdx) as a model of DMD and C57BL/10 mice as controls. Mdx were untreated or orally treated with resveratrol (400 mg/kg/d) for 3 weeks of age. Diastolic left ventricular (LV) thickness (0.72±0.02 vs. 0.82±0.03 mm), heart-to-body weight ratio (4.1±0.6 vs. 5.4±0.8 mg/g), and atrial natriuretic peptide (ANP) mRNA level (4.3-fold) were significantly increased in 40-week-old mdx mice compared with those in the control. Echocardiography showed that diastolic LV posterior wall movement, an index of LV diastolic function, was significantly slower in the untreated mdx than in the controls (21±1 vs. 30±2 mm/sec), though LV dimension and LV ejection fraction were similar in the two groups. Ventricular fibrosis and collagen gene expressions were increased in the mdx group. These phenotypes of mdx mice were significantly suppressed by treatment with resveratrol. Resveratrol reduced myocardial α-actin and α-actin-H3 histone HI levels determined by immunohistochemistry and immunoblot in mdx hearts, indicating activation of SIRT1. Phospho-ERK1/2 and TGFβ1 mRNA levels in mdx hearts were not reduced by resveratrol. However, resveratrol suppressed the protein level of protein of the transcription co-activator p300, a pro-hypertrophic and pro-fibrotic histone/protein acetyltransferase, in the mdx myocardium. In vitro experiments demonstrated that p300 dose-dependently increased ANP promoter activity, which was suppressed by overexpression of wild-type SIRT1. Wild-type SIRT1, but not deacetylase inactive mutant SIRT1, reduced p300 protein level, which was blocked by the proteasome inhibitor MG132. In addition, SIRT1 was found to promote p500 deacetylation and polyubiquitination.

Conclusions: Resveratrol attenuates both cardiac hypertrophy and fibrosis and improves diastolic LV function in the mdx presumably by SIRT1-mediated down-regulation of p300. SIRT1 activation may be a novel strategy in treatment of cardiomyopathy in dystrophin-deficient mice.

P4540
Continuous infusion of the novel chimeric natriuretic peptide cenderitide in the dahl salt sensitive rat model of hypertension and renal dysfunction: evidence for renoprotection
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Purpose: Cenderitide (CD-NP) is a chimeric natriuretic peptide created by fusing the 22 amino acid human C-type natriuretic peptide (CNP) with the 15 amino acid C-terminus of Dendroaspis natriuretic peptide (DNP). The peptide was engineered to have natriuretic, diuretic, antiproliferative, and vasodilating effects through binding of both guanylyl cyclase (GC) B and GC A receptors. Continuous administration of CD-NP is of interest for fluid management in patients with heart failure and impaired renal function. The purpose of this study was to deter-
Antibodies to C-ending (intracellular) fragment of the angiotensin II type 1 receptor and endothelial NO synthase are a principally new classes of reno-protective and diuretic therapy with low doses Tranilast reduces pathological cardiac fibrosis and diuretic function improving kidney dysfunction: implication for cardio-renal syndrome

**Conclusions:** Only 5 of 33 alleged side-effects are actually made more commonly by beta-blockers. Out of 100 patients reporting hyperglycaemia on beta-blockers in only 17 (85% CI 2–32), is that symptom genuinely caused by the beta-blocker; in the remaining 83 it is natural or caused by the information given. Of patients reporting side-effects, the proportion in whom the drug is genuinely the cause is also low for diarrhoea (18/100, CI 5–30), and dizziness (19/100, CI 11–27). Only two side-effects are genuinely caused in the majority of patients: bradycardia (67/100, CI 56–79) and intermittent claudication (59/100, CI 19–98). 23 of 33 alleged side-effects occur equally with drug or placebo. Remarkably, beta-blockers reduce depression (by 35%, p <0.01) and insomnia (27%, p=0.01).

**Conclusions:** Apparent side-effects of beta-blockers in heart failure are overwhelmingly caused not by the drug, but by heart failure itself or nocebo drug information. Realising how few of the patients reporting side-effects are genuinely caused by the medication may assist patients and doctors deciding on trying, or stopping, medication. Listing untrue side-effects in heart failure harms patients through the nocebo effect (if they take it) or worsened outcomes (if they don’t), and wastes consultation resources.
Methods: Twenty-four patients (age 74±9 yrs; left ventricular ejection fraction 40.2±17.6%) with AHF were enrolled and were treated with intravenous low dose hANP. When adequate diuresis was not obtained by 4 hours after administration despite increasing the dose of hANP twice, low dose DA (1-3μg/kg/min, n=12) or low dose furosemide (F, 10-30mg injection, n=12) was randomly added. Serum creatinine, a novel reno-tubular marker, urinary L-type fatty acid-binding proteins (L-FABP) and an oxidative stress marker, urinary 8-hydroxy-2’-deoxyguanosine (8-OHdG) were measured on admission and after additional DA or F administrations.

Results: Heart rate did not change in both groups. Systolic blood pressure decreased significantly in DA and F groups (137±3 to 119±6, P<0.01, 137±1 to 29.4 to 108±3, P=0.007, respectively). Urine volume increased significantly in both groups (fig). Urinary L-FABP and 8-OHdG decreased significantly in DA but not in F (fig). Serum creatinine did not change in both groups.

Figure 1. Urine volume, L-FABP, 8-OHdG

Conclusion: The combination therapy with low doses of hANP and DA might be a reno-protective strategy for AHF management.

P4547 Cardiac iron and function by CMR in thalassemia major patients treated with combined deferiprone and desferrioxamine regimen versus monotherapies: a multi-center, observational and prospective study

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Purpose: Due to the limited data available in literature, the aim of this multicentre study was to prospectively assess in thalassemia major (TM) the efficacy of combined deferiprone (DFP) and desferrioxamine (DFO) regimen versus DFP and DFO in monotherapy by cardiovascular magnetic resonance imaging (CMR) over a follow up of 18 months.

Methods: Among the first 1135 TM patients in the MIOT (Myocardial Iron Overload in Thalassemia) network, we evaluated those who had been received combined regimen (N=51) or DFP (N=39) and DFO (N=74) monotherapies between the two CMR scans. Iron overload was measured by T2* multiecho technique. Biventricular function parameters were quantitatively evaluated by cine images.

Results: The percentage of patients that maintained a normal global heart T2* value was comparable between DFP+DFO versus both groups. Among the patients with myocardial iron overload at baseline, the changes in the global heart T2* and in biventricular function were not significantly different in DFP+DFO versus the DFP group. The changes in the global heart T2* were significantly higher in the DFP+DFO versus both groups, without a difference in biventricular function.

Conclusions: In TM patients at the dosages used in the real world, combined DFP+DFO regimen was more effective in removing cardiac iron load only versus the DFO group. Combined therapy did not show an additional effect on heart function.

P4548 Evaluation of safety, tolerability, PK and hemodynamic properties of JNJ-39588146 (stresscopin) in healthy and HF subjects: a phase 1 ascending dose randomized multicenter trial

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Purpose: JNJ-39588146/human Stresscopin (SCP) is a member of the corti-
corticin releasing factor family of peptides. It is a highly selective agonist of CRFR2. This three part study assessed the safety, PK, and hemodynamics of SCP in healthy subjects (HS) and heart failure (HF) subjects.

**Methods:** In Part 1, 30 male HS were randomized to receive continuous IV infusions of either SCP (0.1 to 144 ng/kg/min, N=25) or placebo (N=5) for 7.5 hours (h), with increases in dose at 2.5 and 5h. In Part 2, 20 subjects with HF with EF < 40% were randomized to receive either SCP (0.3 to 54ng/kg/min, N=13) or placebo (N=7) for 7.5h, with 2 increases in dose. In Part 3, 26 male and female HS were randomized to receive a constant IV infusion of either SCP (54ng/kg/min, N=20) or placebo (N=6) for 24 or 72h. Heart rate (HR) and Cardiac index (CI) were measured by impedance cardiography. HR was noted to decrease during the infusion for placebo subjects. This ‘placebo effect’ was considered when analyzing the HR and CI data for SCP treated subjects.

**Results:** SCP was safe and well tolerated with no notable changes in ECG parameters and no ventricular arrhythmias. The proportion of subjects with AEs who received SCP at doses >36 ng/kg/min was similar to those in subjects receiving placebo. The mean baseline CI in the HS and HF subjects was 3.2 and 2.9L/M2. In HS who received SCP (0.1 to 36ng/kg/min), no notable change in CI, HR, or BP was seen compared to placebo. In HF subjects who received SCP (0.3 to 36ng/kg/min), a higher mean CI (7.15%), was seen compared to placebo. Though numerically lower BP was seen in HF subjects dosed with SCP compared to placebo, no notable change in BP and no dose relationship was observed. At doses >36 ng/kg/min, a dose-related increase in HR was seen in both HS and HF subjects. In HF subjects, the increase in HR was 7.8 bpm at the highest dose (54ng/kg/min) compared to placebo. A greater proportion of subjects who received >36 ng/kg/min of SCP had AEs compared to placebo: the most common AEs in SCP treated subjects were: headache, back pain, feeling hot, nausea, vomiting, and calther site pain or inflammation. In general, SCP showed linear pharmacokinetics as the systemic exposures increased with the infusion rate. The elimination was multi-phasic, with initial rapid decline of SCP (112-10-15 min) followed by a slower terminal phase. No anticoagulation were detected.

**Conclusion:** IV infusions of SCP were safe and well tolerated in HS and HF subjects. SCP showed linear PK that was similar between HS and HF subjects. Overall, the HR, CI and PK data were consistent with pre-clinical findings.

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**Table 1**

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**Conclusion:** Improvement in EF and functional class with MRA therapy are independent of baseline NYHA.

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**Table 1**

<table>
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**Conclusion:** Improvement in EF and functional class with MRA therapy are independent of baseline NYHA.
Continuous furosemide infusion versus furosemide
manitol infusion in acute congestive heart failure

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Background: Loop diuretics remain the cornerstone for fluid mobilization in patients with acute congestive heart failure (CHF) although there is little evidence regarding the ideal dosing strategies and method of administration. Data on the use of mannitol for prophylaxis and/or treatment of acute CHF is controversial and the ideal duration of mannitol infusion is not well defined.

Methods: A retrospective study of 233 patients with CHF [N=108 who received treatment with continuous furosemide-manitol infusion (FM) and N=125 with continuous furosemide infusion] was performed. Infusions were administered intravenously for a period of 1-4 days. Dose titration was protocol-driven and based on urine output. Outcomes of diuresis achieved, death during hospitalization, dialysis requirement, length of hospital stay, effects on kidney function and electrolytes were assessed. Data are reported as mean±SD.

Results: In the comparison of continuous furosemide infusion, there was no significant difference in patients’ weight (4.7±1.9 kg vs. 4.84±2.03 kg, p=0.02) or in the mean creatinine level (0.5±0.3 mg/dl vs. 0.4±0.2 mg/dl, p=0.3), respectively; P=0.45. There was no significant difference between these groups in the need for dialysis (9.6% vs. 9.2%, p=0.98), in hospital death (10.4% vs. 10.1%, p=0.89), duration of hospitalization (6.3±1.2 and 6.0±1.5 days, p=0.1), respectively; P=0.45. There was no significant difference in patients' weight (-4.71±3.52 kg vs 2.8±2.5 kg, p=0.99) and duration of hospitalization (6.3±1.2 and 6.0±1.5 days, p=0.89), respectively; P=0.45. There was no significant difference in the rate of dialysis requirement, length of hospital stay, effects on kidney function and electrolytes assessed. Data are reported as mean±SD.

Conclusions: FM is equally efficacious as furosemide infusion in severe CHF. Mortality continues to be high in CHF patients with underlying kidney failure.

Zofenopril and ramipril plus ASA in post-myocardial infarction patients with left ventricular systolic dysfunction: a post-hoc analysis in preserved or impaired left ventricular fraction at entry

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Background: Concomitant administration of an angiotensin-converting enzyme inhibitor (ACEI) and acetyl salicylic acid (ASA) is a common option in patients with both heart failure and ischemic heart disease. However, the well-known pharmacological interaction between ACEI and ASA may be responsible for a reduction of the positive effect of ACEI on cardiovascular outcomes. In the SMILE-4 Study we have shown a more favorable impact of zofenopril plus ASA than ramipril plus ASA combination on 1-year occurrence of major cardiovascular events in patients with acute myocardial infarction (AMI) complicated by left ventricular dysfunction (LVD). Objective: to compare zofenopril and ramipril efficacy in combination with ASA in a subgroup of patients of the SMILE-4 with preserved (<40%) or impaired (<40%) left ventricular fraction at entry.

Methods: The SMILE-4 was a phase IIIb, randomized, double-blind, parallel-group, multicenter, European study comparing the safety and efficacy of zofenopril and ramipril in ACS patients with preserved (<40%) or impaired (<40%) left ventricular fraction at entry. The study enrolled 4054 patients with preserved LVEF at baseline, in patients with LVD (clinical signs of heart failure or a left ventricular ejection fraction ≤45% following AMI. The primary study end-point was 1-year combined occurrence of death or hospitalization for heart failure or cardiovascular causes. Information on LVEF at baseline was available in 710 out of the 716 patients of the intention-to-treat population.

Results: In the main study population the primary outcome was significantly reduced by zofenopril vs. ramipril (odds ratio, OR and 95% confidence interval, CI: 0.70, 0.51-0.96; p=0.028). Overall, 444 (83.1%) patients had preserved and 262 (56.9%) had impaired LVEF at baseline. In the first group, the rate of major cardiovascular events was significantly lower than zofenopril than under ramipril (22.5% vs. 32.8%; OR: 0.60, 0.39-0.91; p=0.016). This was the case also for the group of patients with impaired LVEF, though between-group difference was not statistically significant (37.7% zofenopril vs. 44.4% ramipril; OR: 0.77, 0.47-1.26; p=0.297). The reduction in the risk of major cardiovascular events was significantly larger (p<0.019) in patients with preserved LVEF at baseline.

Conclusions: This retrospective analysis of the SMILE-4 Study confirmed the superiority of zofenopril plus ASA as compared to ramipril plus ASA in the prevention of long-term cardiovascular outcomes. The benefit was particularly evident in subjects with preserved left ventricular function at study entry.

Treatment effect versus selection bias in systolic heart failure patients receiving higher target doses of ACE inhibitors: Insights from Studies of Left Ventricular Dysfunction (SOLVD) treatment trial

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Background: In RCTs of ACE inhibitors (ACEs) in systolic heart failure (SHF), both ACEIs and placebo were up-titrated to higher target doses if tolerated. The role of this implicit selection bias on mortality remains unclear.

Methods: In SOLVD Treatment trial, SHF (EF ≤35%) patients were randomized to placebo or enalapril. During 2.3 wks post-randomization, study drugs were up-titrated to target doses (≥20 mg/day) in 61% (748/1234) and 57% (696/1224) of pts in placebo and enalapril groups, respectively. Primary outcome was all-cause mortality (median follow-up, 35 mos).

Results: When compared with overall placebo, only target dose enalapril pts had significant mortality reduction (HR, 0.79; 95% CI, 0.68–0.93; p<0.004), However, when compared with dose-specific placebo groups, both target and below-target dose enalapril pts had similar mortality reductions (5% absolute and 10% relative; p for interaction, 0.970; Table). Mortality reduction associated with target dose was similar in both treatment groups (Figure).

Table. All-cause mortality by below-target dose enalapril (vs. below-target placebo) and target dose in placebo (vs. target dose placebo) in the SOLVD Treatment trial

<table>
<thead>
<tr>
<th>Dosages</th>
<th>Events in placebo group</th>
<th>Events in enalapril group</th>
<th>Absolute risk difference</th>
<th>Multivariable-adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below-target</td>
<td>40% (196/486)</td>
<td>35% (185/528)</td>
<td>– 5%</td>
<td>0.90 (0.81–0.998)</td>
</tr>
<tr>
<td>Target</td>
<td>38% (267/706)</td>
<td>33% (263/786)</td>
<td>– 5%</td>
<td>0.90 (0.82–0.98)</td>
</tr>
</tbody>
</table>

Conclusions: Below-target dose enalapril reduced mortality in SHF, and up titration to target dose had little additional treatment effect. Similar mortality reduction associated with target dose of both enalapril and placebo suggest selection bias associated with dose up titration.

Statin therapy and clinical outcomes in acute heart failure patients complicating acute myocardial infarction: insights from the EPHESUS trial

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1INSERM, Center of Clinical Investigation 9591, Loran Institute of Heart and Stroke, Louis Mathew, Nancy, France; 2University of Bari, Bari, Italy; 3University of Kiev, Kiev, Ukraine; 4Monash University, Melbourne, Australia; 5University Medical Center Groningen, Department of Cardiology, Groningen, Netherlands; 6University of Michigan, Ann Arbor, United States of America

Purpose: Several clinical trials have shown that in acute and post-acute myocardial infarction (MI), statin therapy improves cardiovascular (CV) outcomes, but in these trials patients with acute heart failure (HF) were excluded or only few were enrolled. In patients with chronic heart failure (CHF), initiation of statin therapy reduces CV hospitalizations but not all-cause or CV mortality. However, these trials did not investigate whether patients who evolved to HF while being on statin benefited from this therapy. We aimed to assess the association between statin therapy and clinical outcomes in the setting of acute HF with systolic dysfunction complicating acute MI.

Methods: We performed a post-hoc analysis in 6632 patients included in the
Efficacy of ivabradine therapy on right heart parameters and prognosis in patients with severe systolic chronic heart failure

L.R. Tomasany, K.G. Adaman, A.L. Chilingaryan. Institute of Cardiology, Yerevan, Armenia

The aim of study was to assess the efficacy of ivabradine (I, up to 15 mg) therapy on prognosis, right ventricular (RV) and atrial (RA) functional parameters, BNP, NT-pro-BNP and hsCRP levels in patients (pts) with III-IV NYHA FC systolic CHF in sinus rhythm.

Methods: 76 pts (age 57.4) were randomly assigned to group A (n=38, non-receiving I) and group B (n=38, receiving I), in addition to ACE inhibitors, beta-blockers, digoxin and diuretics. Assessment of RV EF, myoccardial mass (MM), myocardial perfusion index (MPI), fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), relative (early and late) atrioventricular apical filling velocities, deceleration time (DT) of E wave, overall filling time (OFT), pulmonary artery (PA) ejection (ET) and pre-ejection (PET) times, RA functional index (Fl) and fractional contribution (FC), BNP, NT-pro-BNP and hsCRP levels was performed at baseline and 12 months.

Results: 1-year mortality, hospitalization rate and combined endpoint of mortality and hospitalization (%) were, respectively, 34.2, 55.3 and 89.5 and 21.1, 31.6 and 89.5 in pts treated with I compared to group A. 1-year treatment with I increased (%) EF at 27.6, FAC at 25, TAPSE at 37.3, E/A at 27.4, index (Fl) and fractional contribution (FC), BNP, NT-pro-BNP and hsCRP levels was performed at baseline and 12 months.

Conclusions: 1) Decrease of BNP, NT-pro-BNP and hsCRP >50%; HR ≤40% and increase of RV EF and E/A at ≥25%, TAPSE ≥50% and RA Fl ≥60% identified pts with cardiac events reduction. 2) Prognostic benefit, associated with use, seems to be related to improvement of right heart parameters, neurohumoral and inflammation status and HR reduction.

Subcutaneous furosemide can prevent hospitalization in fluid overload decompensation of chronic heart failure

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Purpose: Chronic heart failure (CHF) is a high prevalent disease, a main cause of admission and it supposes a high economic cost. The basis of treatment for fluid overload consists of diuretics. Furosemide is the most widespread. When oral treatment is not enough, the endovenous route is the most frequent access, but many times it requires admission. Relevant differences between bolus and perfusion have not been proved. We tested ambulatory continuous infusion of subcutaneous furosemide (SF) with elastomeric pumps in order to prevent hospitalization in patients with fluid overload deccompensation of CHF.

Methods: 25 patients (76% male, 74±10 years old) in 42 episodes of fluid overload were treated by subcutaneous system of furosemide continuous infusion in a heart failure department. Elastomeric pumps with UFA-filter were prepared with different dilutions of furosemide (SF) during 2, 4 or 5 days of infusion. Analytical, clinical and functional data were prospectively registered.

Results: 52% suffered hypertension, 24% diabetes, 36% chronic renal failure, mean creatinine 1.58±0.6, 72% and arterial pressure ≤140/90 mmHg. 71% were on beta-blockers therapy, 81% on angiotensin-converting enzyme inhibitors/angiotensin-receptor-antagonists II and 24% were on aldosterone-antagonist treatment. Mean chronic dose of furosemide was 110±50 mg, 92% were in NYHA class III-IV. 52% had severe left ventricle impairment and 44% severe pulmonary hypertension by echocardiogram. Mean NT-proBNP was 4676±5762 pg/ml. After therapy (9±4 days) with furosemide (150±40 mg), mean weight loss was 2.11±2.9 kg (79.05±76.93 kg, p<0.0002), creatine levels were stable (1.58 vs 1.53, p>0.03) and no clinical relevant hypokaliemia happened (2% (1p) had >3mmEq/l (2.9 mEq/l) but no clinical events). Only 17% (7p) needed hospitalization due to fluid overload during therapy and no deaths during therapy occurred. Main adverse events were local complications at the infusion point without clinical significance (pain 5%, irritation 10%, disconnection 5%, kinked 3%, local infection 7% and local bleeding 3%). NYHA class was improved in 61% of episodes, it did not differ in 37% and it worsen in just 2% (1p).

Conclusion: Ambulatory continuous infusion of subcutaneous furosemide by elastomeric pumps is effective and safe to prevent hospitalization in patients with fluid overload decompensation of CHF. No relevant renal, ionic or clinical complications occurred. Frequent local minor complications were observed. So, this alternative route of diuretic administration could have a beneficial economic impact.

Are there relationships between high resting heart rate and not optimal doses of beta-blockers in patients with systolic heart failure in contemporary Poland? Results of DATA-HELP study

E.A. Jankowska1, B. Kurian2, W. Baniasik3, P. Ponikowski1 on behalf of On behalf of Of DATA-HELP study (Diagnostic And Therapeutic methods, used in patients with systolic HEart failure. Living in Poland) investigators.

1Wrocław Medical University, Department of Cardiology, Wrocław, Poland; 2Merok, Warsaw, Poland; 3Centre for Heart Diseases, Military Hospital, Wrocław, Poland

Background: Resting heart rate (HR) is associated with poor outcome, and its reduction to both β-adrenergic and II current blockade has provided survival benefits in patients with systolic heart failure (HF). The magnitude of contemporary European population of patients with systolic HF and high HR, and links between applied therapy and achieved HR in everyday practice are unclear.

Methods: Registry DATA-HELP was performed in X–XI 2009 in Poland in a randomly selected representative sample of 5563 outpatients with clinical diagnosis of HF and LVEF<45%; resting HR was available in 5513 subjects (99%).

Results: We analysed 3620 patients with systolic HF in a sinus rhythm (65% of the whole cohort) (age: 66±11 y, BMI: 28.2±4.2 kg/m², men: 64%, NYHA class III-IV: 31%, previous MI: 61%, diabetes: 33%). Mean±SD HR was 75±13 bpm, median with lower/upper quartiles 72 (68-80) bpm, HR >70 bpm and ≥75% were found in 68% and 47% of patients, respectively, with increasing frequency along NYHA classes (III/IV/III-IV-HR >70 bpm: 65%/7%74%/77%, HR >75 bpm: 42%/45%/51%/60%, both p<0.001). In a multivariable stepwise model, high HR was related to high syst BP (p<0.001), presence of pulmonary congestion (p<0.05) and peripheral oedema (p<0.001), advanced NYHA class (p<0.01), older age (p<0.001). Among variables in the entire cohort, HR >75 bpm was associated with higher mortality (Hazard ratio: 1.57 at cycle III vs cycle I p<0.001). In 62% of patients received β-blockers: bisoprolol, carvedilol, metoprolol, nebivolol and others were used in 52%, 30%, 12% and 3% of subjects, respectively, in an average daily doses of 5.4±3.9, 21.5±14.1, 63.2±37.1, 4.4±1.5 mg, respectively for 4 major β-blockers (i.e. 41±34% of daily recommended dose). There were no differences in HR between those treated vs not treated with β-blockers, and between those treated with different β-blockers (all p<0.2). There was no association between HR and the % of daily recommended dose, and there were no correlations between HR and the daily dose of bisoprolol, metoprolol, nebivolol (analysed separately) (all p>0.2). There was an inverse relationship between HR and the daily dose of carvedilol, which remained significant after adjustment for clinical status (p<0.05).

Conclusions: Polish registry demonstrates high prevalence of increased resting HR and low doses of β-blockers used in outpatients with SHF in a sinus rhythm, and no relationship between HR and the dose of β-blockers (in spite of carvedilol). HR is not sufficiently controlled in the majority of these patients, and it is reliable to consider also alternative therapies reducing HF (e.g. ivabradine).

Do early and late nephroprotective effects differ with different inhibitors of renin-angiotensin-aldosteron system in chronic heart failure patients?

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Purpose: To compare the extent of nephroprotection in chronic heart fail-
ure (CHF) patients treated with angiotensin-converting enzyme inhibitor (ACEI), angiotensin-II receptor blocker (ARB), and direct renin inhibitor (DRI).

Methods: 155 patients with CHF of different etiology and NYHA class II or III, with chronic kidney disease (CKD) stage I to III, and with uncorrected arterial hypertension, were randomized after getting informed consent into three treatment arms: 1st – with ACEI enalapril (n=49), 2nd – with ARB losartan (n=47), and 3rd – with DRI aliskiren (n=59). The patients were evaluated at baseline, after two weeks and after one year of treatment, for systolic and diastolic blood pressure (BP), microalbuminuria (MAU), and glomerular filtration rate (GFR) by Cockcroft-Gault equation. Overall there were 6 drop-outs from groups due to patients’ decision and no cross-over of assigned treatment arms at follow-up. Mean daily doses at one year evaluation were 19.1 mg for enalapril, 65.4 mg for losartan, and 27.4 mg for aliskiren. All patients were on beta-blockers and aldosterone antagonists, and 86% on diuretics in comparable doses. ANOVA for independent and dependent samples was used for statistical analysis with 0.05 alpha error cut-off.

Results: After one year of treatment there was no significant difference between groups in achieving BP control: BP < 140/90 mm Hg was observed in 65.8±6.8% of patients in the 1st group, 72.8±6.5% in the 2nd, and in 73.1±6.8% in the 3rd. Slight decrease in MAU (by 24.2±27.7 mg/day) was already seen after two weeks of treatment; it became more pronounced and statistically significant (p<0.05) at one year evaluation within each group but more or less similar between the respective groups: by 66.3±2.1 mg/day and 71.2±2.9 mg/day vs 62.6±3.9 mg/day. Ten-day higher GFR was also noted in two weeks in all groups, and reached statistical significance in each group up to one year. At one year evaluation, however, there was no significant difference between losartan (by 11.2±1.3 ml/min) and enalapril (by 5.4±1.2 ml/min). There was only a tendency for higher nephroprotection of aliskiren over losartan after one year of treatment. Tolerance of drugs was good in all treatment arms. There was only a tendency for higher nephroprotection of aliskiren over losartan after one year of treatment. Tolerance of drugs was good in all treatment arms.

Conclusion: In CHF patients with CKD and arterial hypertension the nephroprotective effects may differ with different types of renin-angiotensin-aldosterone system inhibition, being somewhat greater in terms of higher GFR with aliskiren and losartan as compared to enalapril after one year of treatment.

Effect of valsartan and amlodipine on heart failure and left ventricular mass in Japanese hypertensive patients with glucose intolerance: a subanalysis of the Nagoya heart study

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Purpose: The Nagoya Heart Study was a multicenter, prospective, randomized, open labeled, blinded endpoint trial that was performed to compare the beneficial effects of valsartan and amlodipine on cardiovascular events in Japanese hypertensive patients with glucose intolerance without apparent heart failure. Although blood pressure levels were well controlled in both groups and remained similar throughout the trial, valsartan had more favorable effect on heart failure than amlodipine.

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ence of unknown dyslipidemia was high in the population (34.9%); only 7.2% of the participants with dyslipidemia were treated sufficiently.

Conclusions: These current data show a surprisingly high proportion of individuals being not aware of prevalent CVRFs. If known, risk factors are still often untreated or treated insufficiently. These data indicate a great potential in reducing cardiovascular disease burden by improving the detection and treatment of classical CVRFs.

**P4655**

**Use of lipid lowering therapy in primary care across Europe: results from the European study on cardiovascular risk prevention in daily practice (EURIKA)**

- D. Baldassarre2, E. Tremol2, S.E. Humphries3, J.F. Frostegård1, U. De Faire1

Methods: The European Study on Cardiovascular Risk Prevention and Management in Daily Practice (EURIKA) was a cross-sectional study conducted simultaneously in 12 European countries from May 2009 to January 2010. It recruited 1,641 patients aged 50 years or older who were free of cardiovascular disease or who had mild to moderate hypercholesterolemia in a placebo-controlled, randomized, double-blind intervention lasting for six months.

Purpose: The aim of the present study was to investigate the association of low levels of anti-PC with the uptake of oxidized LDL and inhibit the effect of inflammatory phospholipids, thereby exerting an atheroprotective effect. Previous studies have shown that low anti-PC serum levels increase the risk of cardiovascular (CV) events. The aim of the present study was to investigate the association of low levels of anti-PC with the incidence of CV events and the progression of intima media thickness (IMT) in a large population of individuals with or without diabetes mellitus (DM) or obesity. The primary outcome was the composite of cardiovascular death and cardiovascular hospitalization for coronary or cerebrovascular events. Cox proportional hazards regression models were used to calculate multivariable-adjusted hazard ratios (HR) and confidence intervals (95%-CI) in time-to-event analyses. In the total cohort and in patients with DM or obesity, neither fasting nor postprandial TG predicted event-free survival independently. After stepwise adjustment for baseline characteristics, carbohydrate risk factors, and metabolic parameters, fasting TG >150mg/dl (compared to <106mg/dl) were independently associated with event-free survival in normoglycemic and IGT patients (NoDM: HR 3.50, CI 1.01-10.94, p=0.04; Lean: HR 1.33, CI 1.00-1.75, p=0.02). The area under the curve (AUC) is an integral measure of serum triglycerides from fasting to the postprandial TG peak. An AUC above 1120mg/dl (compared to ~750mg/dl), also predicted risk independently (NoDM: HR 2.62, CI 1.00-6.98, p=0.05; Lean: HR 3.12, CI 1.00-9.81).

Conclusions: In normoglycemic, non-obese CAD patients, both, fasting and postprandial TG independently predict cardiovascular outcomes. The findings of the study are of great clinical relevance with respect to the identification of high-risk patients, who may benefit from TG-lowering therapies.

**P4657**

**Fasting and postprandial triglycerides are independent cardiovascular risk markers in non-obese coronary artery disease patients with normal glucose tolerance**

- C. Werner1, S. Groenewold1, M. Fritsch1, A. Filmer1, S. Graebner2, M. Boehm1, U. Laufs1, Universitätsklinikum des Saarlandes - Klinik für Innere Medizin III, Homburg, Germany; 2 Saarland University Hospital, Institute for Medical Biometry, Epidemiology and Medical Informatics, Homburg, Germany

Methods: An oral triglyceride (OTT, 75g cream fat) and glucose tolerance test (OGT, 75g glucose) was developed to obtain standardized measurements of postprandial TG in an observational, prospective study on 514 consecutive patients (83% male, 95% on statin) with angiographically confirmed stable coronary artery disease. Patients with medical treatment for diabetes mellitus (DM) received the OTT only; all others ingested the OTT and the OGT 3 hours later in a sequential test protocol. Lipid and glucose parameters were measured at fasting, 3, 4, and 5 hours after the OTT/OGT.

Results: Metabolic characterization revealed that 126 patients had normal glucose tolerance (NoDM), 388 had impaired glucose tolerance (IGT) or DM, 95 patients had a normal BMI (<25kg/m²), and 419 were obese. Both, IGT/DM and obesity were associated with elevated fasting and postprandial triglycerides. Follow-up was 24 months and the primary outcome was the composite of cardiovascular death and cardiovascular hospitalization for coronary or cerebrovascular events. Cox proportional hazards regression models were used to calculate multivariable-adjusted hazard ratios (HR) and confidence intervals (95%-CI) in time-to-event analyses. In the total cohort and in patients with DM or obesity, neither fasting nor postprandial TG predicted event-free survival independently. After stepwise adjustment for baseline characteristics, carbohydrate risk factors, and metabolic parameters, fasting TG >150mg/dl (compared to <106mg/dl) were independently associated with event-free survival in normoglycemic and IGT patients (NoDM: HR 3.50, CI 1.01-10.94, p=0.04; Lean: HR 1.33, CI 1.00-1.75, p=0.02). The area under the curve (AUC) is an integral measure of serum triglycerides from fasting to the postprandial TG peak. An AUC above 1120mg/dl (compared to ~750mg/dl), also predicted risk independently (NoDM: HR 2.62, CI 1.00-6.98, p=0.05; Lean: HR 3.12, CI 1.00-9.81).

Conclusions: In normoglycemic, non-obese CAD patients, both, fasting and postprandial TG independently predict cardiovascular outcomes. The findings of the study are of great clinical relevance with respect to the identification of high-risk patients, who may benefit from TG-lowering therapies.
Methods: The subjects replaced 20 g/d of their regular fat intake with the test spread with (stost group) or without (controls) plant stanol esters (3 g/d of plant stanols). Compliance was verified with measuring serum plant stanols. Arterial stiffness was measured using the pulse wave velocity and the obtained variables were carotid-ankle vascular index (CAVI) and augmentation index (AI), and endo- 
dothelial function was measured as reactive hyperemia index (RHI) using peri-
pheral arterial tonometry. Serum sterols were analyzed with gas-liquid chromatog-
raphy. The study was performed according to the principles of the Declaration of Helsinki of the World Medical Association, and the Ethics Committee of the Hospital District of Helsinki and Uusimaa had accepted the study protocol.

Results: The mean age of the study population was 50.8±1.0 (SEM) years with 38% of males. At baseline, mean LDL cholesterol was 3.5±0.1 mmol/L, HDL cholesterol and serum triglycerides were within the reference values, CAVI was 8.7±0.1, AI 9.1±1.9, and RHI 2.2±0.1, respectively. The intervention was well tolerated without any side-effects, and compliance was good. LDL cholesterol was reduced in the stost group by 7.9±1.6% from baseline and by 10±2.2% from controls (P<0.05 for both). AI changed significantly differently between the groups: it was increased in the controls and decreased in the stost group (P=0.04 between groups). CAVI was decreased in men with stost by 1.1±1% and increased in control men by 3.2% so that the difference was significant (P<0.05). In the stost group, the change in RHI was inversely related to the change in LDL cholesterol level suggesting that the more LDL cholesterol was reduced, the more RHI increased (r=-0.452, P=0.006). 

Conclusions: Six-month consumption of 3 g plant stanols as esters decreased arterial stiffness and increased endothelial function by reducing LDL cholesterol by 10% compared with controls. This study is dedicated to the memory of Professor Tatj A. Miettinen.
Comprehensive assessment of diastolic function in patients with hypertrophic cardiomyopathy

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Purpose: To assess the value of velocity and flow rate related parameters obtained by cardiac magnetic resonance (CMR) for evaluation of left ventricular (LV) diastolic function in patients (pts) with hypertrophic cardiomyopathy (HCM).

Methods: CMR was performed in 26 HCM pts and 24 healthy volunteers (HV) matched for age, gender, body surface area (BSA) and blood pressure. Diastolic parameters were obtained using a semi-automated software enabling extraction of transmitial flow, including transmitial E and A flow rate peaks, isovolumic relaxation time (IVRT) and early peak diastolic longitudinal myocardial velocity E' obtained using 2D phase contrast-CMR. LV mass and volumes and left atrial (LA) volume (VT) – Philips were measured from cine CMR images.

Results: Mean age was 47.0±20.2 years in HCM pts and 47.5±16.1 in HV (p=NS). LV mass, mass/end-diastolic volume and LA volumes were increased in HCM pts. The ratio between areas of the peaks of IVRT was found in 20 HCM pts. While there was no significant difference in E/A in LV myocardial longitudinal velocity E' and LA emptying fraction were markedly lower in HCM pts. Furthermore, E/E' ratio and late diastolic atrial filling (DT) were higher in HCM pts. There was a linear relationship between increased LV mass and increased LA volumes (p<0.001). IVRT (p=0.003), DT (p=0.002), E/E' (p=0.002) and decreased E' (p=0.003) independent of age, gender and BSA.

Conclusion: Comparison of HCM pts with HV by CMR showed significantly altered LV diastolic function and increased LA volumes related to increased LV mass. Assessment of diastolic function may be considered for routine comprehensive evaluation of left heart function in HCM.

High energy myocardial metabolism in patients with different causes of left ventricular hypertrophy by 31P magnetic resonance spectroscopy

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Purpose: To assess the state of myocardial energy metabolism in patients with arterial hypertension (AH) and left ventricular hypertrophy (LVH) and patients with hypertrophic cardiomyopathy (HCM) compare with healthy volunteers by 31P magnetic resonance spectroscopy (31P-MRS).

Methods: The study included 52 people: group I - patients with AH and LVH (16), group II - patients with HCM (16), group III - relatively healthy volunteers (20). The average age in the groups I and II were 57±5.9 years and 54±6.3 years, respectively, which were not significantly different from each other and group III - 55±6.7 years (p<0.05). ECG-synchronized single voxel 31P MRS was performed on high field MRI system Siemens 3T. The measurements were performed in a double tuned surface coil placed on the chest wall. The localization was done by ISIS. Voxel size was fixed on 92 mm3. The standard protocol was consist 128 repetitions and repetition time was 10,000 ms. The energy index - the ratio between areas of the peaks of phosphocreatine and adenosinetriphosphate (PCr/ATP) was used to evaluate myocardial energy metabolism alterations.

Results: In group I all patients showed symmetrical hypertrophy of the left ventricle, interventricular septum (IVS) thickness was 15±0.12 mm. In group II patients showed asymmetrical hypertrophy, with thetmost pronounced thickening of the IVS, which thickness (17.8±0.24 mm) was significantly different from group I, p<0.05. The IVS thickness in group III was 7.8±0.12 mm. The lowest index value of PCr/ ATP was detected in patients with HCM - 1.32±0.35, which was significantly lower than the index in patients with AH and LVH - 1.76±0.29, p<0.05. The highest index value was recorded in a group of healthy volunteers - 2.18±0.32, which was significantly higher than the values in the groups I and II.

Conclusions: 31P MRS revealed signs of myocardial energy metabolism alteration in patients with LVH. The greatest changes are detected in HCM: patients with AH and LVH also demonstrate a significant reduction in the energy index.
Late gadolinium enhanced cardiac magnetic resonance in lamin A/C, cardiac troponin T and myosin binding protein C gene mutation related cardiomypathies: characteristics and clinical associations

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Purpose: To investigate the correlation between characteristics of late gadolinium enhancement (LGE) in asymptomatic and symptomatic carriers of known cardiomyopathies: characteristics and clinical associations

Methods: Thirty-eight patients with known gene mutations (A/C (LMNA), cardiac troponin T (TNTN2) or myosin binding protein C (MYBPC3)) were included. LGE was assessed in patients with known gene mutations, most prominently expressed with basal and/or mid-ventricular septal wall abnormalities. The LGE characteristics were compared with those of asymptomatic control patients.

Results: LGE was more frequent in LMNA patients (57%) than in those with known mutations in MyBPC3 carriers (30%) and TNTN2 carriers (15%). The wall patterns of LGE were seen in endocardium enhancement in LMNA carriers, midwall patterns of LGE were seen in MyBPC3 carriers, and midventricular septal wall were the most commonly seen pattern in all gene mutations (57% of all LGE positive cases).

Conclusion: The LGE patterns were significantly more frequent in LMNA carriers than in MyBPC3 or TNTN2 carriers. LGE was more frequent in LMNA carriers than in carriers of known mutations in MyBPC3 or TNTN2 carriers. LGE was more frequent in LMNA carriers than in carriers of known mutations in MyBPC3 or TNTN2 carriers.
Poster Session 6: Arrhythmia Mechanisms and Antiarrhythmic Drugs

P4690 Ranolazine modifies the electrophysiological effects of acute myocardial stretching

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Purpose: Mechano-electrical feedback is an arrhythmogenic factor and several mechanisms have been implicated in this effect, involving the stretch-activated ion channels, autocrine/paracrine events or the activation of beta-adrenergic receptors as a result of the stretch-mediated release of catecholamines from intramyocardial nerve endings. Ranolazine inhibits the late inward 
Na+ current, but we do not know whether it also modulates the electric responses to myocardial stretch in acute ventricular stretching produces modifications on the cardiac electrophysiological properties such as an increase of dominant frequency (DF) during ventricular fibrillation (VF). The aim of this study is to analyze and to compare the action of ranolazine (50μM) during stretch-mediated activation frequency under the influence of this drug.

Methods: In eighteen Langendorff-perfused rabbit hearts VF recordings were obtained using epicardial multiple electrodes on the left ventricle free wall under stretch (n=9) and during perfusion of ranolazine (5μM) (n=9). DF was induced by pacing at increasing frequencies, without interrupting coronary perfusion. After the induction of VF, stretching was applied and maintained for ten minutes and after this period, local stretching was suppressed. DF during VF was determined using spectral techniques and spectral concentration (SpConc) was calculated as a percentage of the total energy contained in the interval of DF=0.5 Hz.

Results: In control series, myocardial stretch increased DF of VF from 13.6±2.3 Hz to 19.1±3.1 Hz (p=0.001), with a SpConc that decreased from 29.8±8% to 18.3±3% (p=0.001). These parameters returned to baseline values 3 minutes after stretch (DF=13.1±2.4 Hz, ns, and SpConc=28.8±7%, ns). In ranolazine group, DF prior to stretch was 11.4±1.6 Hz (p=0.053 vs control), and the SpConc was 25.4±5 (ns vs control). During myocardial stretch DF increased to 14.5±2.4 Hz (p=0.012 vs baseline and p=0.0001 vs control), with a SpConc of 23±4% (ns vs baseline and p=0.01 vs control). After suppressing stretch, DF returned to values similar to baseline state (10.8±1.3 Hz, ns vs baseline, and p=0.034 vs control), with a SpConc of 28±4% (ns vs baseline and vs control). The maximum DF percentage increment obtained in the control group during stretch was 41% versus 23% in the ranolazine group, being the latter percentage significantly lower than in control group.

Conclusion: The inhibition of the late inward 
Na+ current with ranolazine reduces the ventricular electrophysiological modifications produced by acute myocardial stretching.

P4691 Novel electrophysiological properties of dronedarone: Inhibition of human cardiac two-pore-domain potassium (K2P) channels

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Purpose: Dronedarone is currently used for the treatment of paroxysmal and persistent atrial fibrillation (AF). Pharmacological inhibition of cardiac two-pore-domain potassium (K2P) channels results in action potential prolongation and has recently been proposed as novel antiarrhythmic strategy. We hypothesized that blockade of human K2P channels contributes to the electrophysiological efficacy of dronedarone in AF.

Methods: Two-electrode voltage clamp electrophysiology was used to record K2P currents from Xenopus oocytes.

Results: All functional human K2P channels were screened for dronedarone sensitivity, revealing significant and concentration-dependent inhibition of cardiac K2P2.1 (IC50 = 26.7 μM) and K2P3.1 channels (TASK1, IC50 = 18.7 μM) with maximum current reduction of 60.3% and 65.5%, respectively. The molecular mechanism of action was studied in detail. Dronedarone block was voltage-independent and affected open and closed channels. K2P3.1 currents were reduced in frequency-dependent fashion in contrast to K2P2.1. Mutagenesis studies revealed that amino acid residues implicated in K2P3.1 drug interactions were not required for dronedarone blockade, indicating a novel pharmacological binding mode.

Conclusions: The class III antiarrhythmic drug dronedarone targets multiple human cardiac two-pore-domain potassium channels, including atrial-selective K2P3.1 currents. K2P current inhibition by dronedarone represents a previously unrecognized mechanism of action that is expected to suppress AF by prolonging atrial refractoriness in vivo.

P4692 Mechanisms of antiarrhythmic activity of new class III agent Niferidile in patients with supraventricular arrhythmias


Background: Niferidile (NI) is a new potassium channel blocker that inhibits transient outward and delayed rectified currents. Preclinical studies showed that NI increases effective refractory periods (ERP) in atria more than in ventricles. High affinity of NI to atrial myocardium is thought to contribute to high efficacy in supraventricular arrhythmias and to low risk of ventricular proarrhythmia.

Objectives: To evaluate electrophysiological mechanisms of antiarrhythmic effect of NI in patients with paroxysmal supraventricular tachycardia (PSVT).

Materials and methods: Effects of NI (20 μg/kg intravenously) were studied in 24 patients (14 males) with PSVT (12 orthodromic tachycardia in WPW syndrome, 8 AV-nodal reentrant tachycardia, 4 orthodromic tachycardia due to concealed bypass tract) during endocardial electrophysiological study. Termination of sustained paroxysms of SVT by NI could be investigated in 18 patients and prevention of resurgence of PSVT in 22 patients.

Results: NI terminated PSVT in 77.77% and prevented reinduction in 72.72% of patients. NI increased ERP of right atrium (by 22.88%), left atrium (by 20.09%), right ventricle (by 12.33%) and accessory pathways (antegrade by 21.47%; retrograde by 32.83%). NI did not affect sinus node and atrioventricular conduction. NI significantly increased relative refractory period (RPP) of His-Purkinje system (by 33.41%), NI prolonged QT (by 24.5%; p<0.01) and QTC (by 17.31%; p<0.05) intervals. One patient developed short runs of torsade de pointes shortly after injection of drug.

Conclusions: Prolongation of ERP, predominantly in atria and accessory pathways, and RRP in His-Purkinje system are main electrophysiologic effects of NI. New drug showed high antiarrhythmic efficacy and good safety profile in patients with PSVT.
Arrhythmia mechanisms and antiarrhythmic drugs / Arrhythmia mechanisms

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Value-based pricing for dabigatran, rivaroxaban and apixaban in patients with non-valvular atrial fibrillation in Germany

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Warfarin effectively reduces the incidence of ischemic stroke in patients with non-valvular atrial fibrillation (AF) but increases the risk of major and intracerebral bleeding, myocardial infarction, and mortality were taken from dabigatran's RE-LY (D110 and D150), rivaroxaban's ROCKET (R20), and apixaban's ARISTOTLE trials (A5). All were randomized and prospective trials and compared the NOAC with dose-adjusted warfarin including more than 6.000 participants. The quality-adjusted life years (QALYs), costs (in Euro 2012 for Germany), and incremental cost-effectiveness ratios (ICER) for the NOACs were calculated with adjusted dose-warfarin as comparator. The societal willingness to pay was set conservatively at 50.000 Euro per QALY. A Markov decision model was adopted using the Tree Age Pro 2011 program. The current daily cost of D110, D150, and R20 in Germany account for about 3.20 Euro. The relation of QALYs was 11.53/11.41 for D110/warfarin, 11.66/11.41 for D150/warfarin, and 11.74/11.5 for A5/warfarin. Total costs were higher for all NOACs compared to warfarin. With this calculations ICER was found for all NOACs in a range of about 50.000 Euro per QALY. Provisionally calculated cost-savings and reduced prices for the NOACs compared to dose-adjusted warfarin ranged from 1.25 Euro to 2.50 Euro per day. Our results are robust in a wide range of sensitivity analyses. The daily value-

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Network meta-analysis of efficacy and safety of dabigatran, rivaroxaban and apixaban in patients with non-valvular atrial fibrillation

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The three new oral anticoagulants (NOAC) dabigatran, rivaroxaban, and apixaban showed equivalent efficacy and safety compared to warfarin in patients with non-valvular atrial fibrillation. A head-to-head clinical trial comparison of these NOACs is highly unlikely to be performed given the expense of such an investigation. Therefore, there is a need for an unbiased comparative assessment of the benefits and risks of the NOACs, based on the available trial data. Appropriate statistical tools for such an analysis is a mixed treatment comparison (MTC) network meta-analysis (NMA). A NMA of the 3 new oral anticoagulants was performed extracting the data of the RE-LY study of dabigatran 110 mg bid and dabigatran 150 mg bid, the ROCKET trial of rivaroxaban and the ARISTOTLE trial of apixaban for the composite outcome of ischemic stroke and systemic embolism with the same intracerebral bleeding mortality and myocardial infarction. The NMA was performed to compare these endpoints using odds ratios and confidence intervals. Dabigatran (150 mg bid) showed superior efficacy in preventing ischemic stroke plus systemic embolism to dabigatran (110 mg bid, p=0.0386) and rivaroxaban (p<0.008). Apixaban had equivalent efficacy with rivaroxaban and dabigatran (either dose). Apixaban was safer (less major bleeding) than dabigatran (150 mg bid, p=0.0036) or rivaroxaban (p<0.0002). Intracerebral hemorrhage occurred with equal frequency for all agents and regimens except for rivaroxaban (higher risk than dabigatran 110 mg bid, p=0.0070). Myocardial infarction occurred less frequently with rivaroxaban and apixaban compared to either dose of dabigatran (all p<0.05). All-cause mortality was not different for any agent or regimen. In the absence of head-to-head comparisons, this network meta-analysis suggests that apixaban and dabigatran at 110 mg bid may offer the best benefit-risk balance for stroke prevention in non-valvular atrial fibrillation. dabigatran 150 mg bid may be preferred for patients with a high risk for embolism.

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Administration of vernakalant in a highly sensitive model of proarrhythmia caused by prolongation of mycardial repolarization without increased vulnerability to arrhythmias

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Purpose: Vernakalant (VER) is a novel and relatively atrial-selective antiarrhythmic drug that inhibits potassium and sodium channels frequency-dependent. Previous studies demonstrated conversion of atrial fibrillation (AF) to sinus rhythm induced by VER. The present study investigated if VER in escalating high doses in a highly sensitive rabbit model of proarrhythmia.

Methods: Eight endo- and epicardial monophasic action potentials (MAP) and two atrial action potentials were continuously at baseline conditions and from 7 rabbits treated with VER, compared to 13 rabbits treated with sotalol (SOT).

Results: Administration of VER (10 μM and 30 μM) showed a significant prolongation of QT-interval compared with baseline (10 μM: +5 ms, 30 μM: +51 ms, p<0.05) and an enhanced action potential duration (APD90, 10 μM VER: +18 ms; 30 μM VER: +20 ms). APD90 prolongation was accompanied by a distinctive influence in effective refractory period (ERP, 10 μM: +40 ms, 30 μM: +50 ms, p<0.05) leading to a significant increase in postrepolarization refractoriness (PRR) defined as the difference between the ERP and APD90 (10 μM: +23 ms, 30 μM: +34 ms, p<0.05). Dispersion of repolarization was not altered by VER. Intraday variability in hearts with mechanical function. In rabbit and swine, reduced potassium concentrations did not lead to early afterdepolarizations (EAD) or polymorphic ventricular tachycardia despite significant QT-prolongation. Application of SOT (100 μM) caused prolongation of QT-interval (+52 ms) and torsades de pointes (TdP) along with an increased ERP (49 ms) and PPR (+15 ms). In contrast to VER, SOT enhanced dispersion of repolarization (+19 ms, p<0.05) and evoked EAD in 12 of 13 rabbits and torsades de pointes (TdP) in 9 of 13 rabbits after lowering of potassium level.

Conclusions: The present study shows that administration of SOT and VER caused comparable prolongation of myocardial repolarization. PRR was increased by both drugs. In contrast to SOT, VER did not affect dispersion of repolarization nor generate EAD and thus did not provoke ventricular tachyarrhythmias. In summary, administration of VER seems to be safe despite significant prolongation of QT-interval.

ARRHYTHMIA MECHANISMS

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F 16915 prevents heart failure induced atrial structural remodelling: a promising new drug as up-stream therapy for atrial fibrillation

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Atrial fibrillation (AF) is a common complication of heart failure and hypertension. By reduction of structural remodelling, upstream therapy is known to prevent the promotion and propagation of AF. However, the existing drugs remain only partially active certainly due to their weak efficacy against atrial remodelling and therefore, a new generation of complicated is required. The aim of the present study is to test the hypothesis that a new pure docosahexaenoic acid derivative, F 16915 would reduce atrial remodelling in a rat model of heart failure induced by 30 min occlusion of left descending coronary artery and 2 months reperfusion. F 16915 (100 mg/kg) was administered by gavages every day after occlusion. The left ventricular function and left atria size were quantified by echocardiogram at each month. The % of shortening fraction in the F 16915 group was significantly restored after 2 months (29.2±4.7% vs 19.6±3.4%, n=9 in the vehicle group P<0.001 compared to 40.3±3.1% in sham group). Despite a marked tendency, the dilation of the left atria was only partially reduced (4.7±0.2 mm in drug F 16915 group vs 5.3±0.2 mm in the vehicle group compared to 4.2±0.1 mm in the sham group). Phosphorylation of connexin-43 (Cx43) was visualised by immunofluorescence in rat atria at the end of the study and quantified using the image j software. F 16915 partially reduced the de-phosphorylation of Cx43 (10.6±1.6 u.a in F 16915 group vs 8.2±1.0 u.a in the vehicle group compared to 11.8±1.3 u.a in the sham group) This protective effect of F 16915
was not associated with significant modification of any hemodynamic parameters. Ventricular infarct size was determined at the end of the experiment and was assessed by histological analysis (Masson staining). F 16915 significantly reduced the extent of infarct size (31.3%, n=9 vs. 46.0%, n=8; p<0.01). In conclusion, in an ischemia-induced heart failure model in the rat, F 16915 prevented the structural remodelling of the left atria associated with an increased left ventricular function. Therefore, F 16915sits new emerging opportunity as up-stream therapy for the treatment of AF.

### Zooming in on the focus: flecainide inhibits atrial fibrillation maintained by aconitine

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**Background:** The contribution of focal discharges for the maintenance of atrial fibrillation (AF) is under discussion. Aconitine (Aco) is used in a model for focal AF. To find mapping criteria for focal discharges during AF, we performed high density mapping of AF maintained by Aco and investigated the effect of flecainide.

**Methods and results:** In open chest experiments in goats (n=6), we performed high density en-docardial mapping to investigate the interaction of focal tachycardias induced by Aco with activation pattern during AF. The topical application of ACO containing crystals on the left atrium in the middle of the mapping area induced rapid focal discharges with radial spread of activation exactly at the place of ACO-application.

Four rapid focal discharges with radial spread of activation exactly at the place of ACO-application occurred at the epicardial coupling intervals of 12.1±0.5 ms respectively vs. 133±6.5 ms, p<0.05. During AF, more than 80% of all local electrograms at the side of breakthroughs showed R-waves, but just 44% of epicardial coupling intervals of breakthroughs and dominant interval at the side of breakthroughs occurred remote from the site of ACO-application. The mean of epicardial coupling intervals of breakthroughs and dominant interval at the site of earliest activation did not show R-waves. S1S1-stimulation (basic cycle length BCL=200 ms) showed that the atrio-ventricular refractory period (AERP) was slightly prolonged in CAP2gt/+ (33.1±5.8 ms) compared to WT (26.7±5 ms, n.s.). During experimental period of 30 min. after ACO-application, neither atrial effective refractory period (BCL=200 ms; 133±2.5 ms vs. 133±6.5 ms, n.s.) nor left atrial vulnerability was changed significantly. Episodes of burst-induced AF became longer (470±88 ms) compared to Aco (242±15 ms). Local electrograms at the site of earliest activation did not show R-waves. T1S1-stimulation (BCL=200 ms) showed that the atrio-ventricular refractory period (AERP) was slightly prolonged in CAP2gt/+ (33.1±5.8 ms vs. 133±6.5 ms, n.s.). During AF the number of breakthroughs increased more than 10-fold (1.4±0.14 per cycle vs. 0.0±0.03 per cycle, p<0.01). Breakthroughs occurred remote from the site of ACO-application. The mean of epicardial coupling intervals of breakthroughs and dominant interval at the site of earliest activation did not show R-waves, but just 44% of them could be explained by transmural conduction (contralateral activation within 8ms). Flecainide inhibited ACO-induced rapid focal discharges at the site of ACO-application. After flecainide, AF was not inducible anymore. Summary: Topical application of flecainide inhibited ACO-induced rapid focal discharges with radial spread of activation exactly at the place of ACO-application. However, the sites of breakthroughs during AF application were slightly different from those of controls.

### Absence of cyclase-associated protein 2 leads to marked atrial and ventricular conduction delays and ventricular arrhythmias

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**Purpose:** Cyclase-associated protein 2 (CAP2) is an evolutionarily conserved protein that plays a major role in regulating the actin cytoskeleton and in signal transduction. CAP2 is predominantly found in the nucleus of undifferentiated cardiomyoblasts and at the M-line of adult cardiomyocytes. Recent studies showed that the expression of CAP2 by a gene trap approach (CAP2gt/gt) results in right ventricular cardiomyopathy and increased mortality in a mouse model. We hypothesised that CAP2 also has a major impact on cardiac electrophysiological parameters.

**Methods:** We performed in vivo electrophysiological studies using right heart catheterisation in 25 mice (8 CAP2gt/gt, 8 CAP2+/- and 9 wild type control mice (WT)) at the age of 14 weeks. We analyzed standard ECGs and electrophysiological parameters and the inducibility of arrhythmias.

**Results:** In comparison to WT, CAP2gt/gt showed a reduction in basal heart rate (480±39.3/90 ms vs. 445.3±34/30 ms, p=0.03), prolongation in PQ time (40.5±3.6ms vs. 39.0±1.6ms; p=0.02), 26 ms lower in CAP2gt/gt. QRS time (23.1±1.3ms vs. 21.7±1.3ms; p=0.002) was significantly shorter in CAP2gt/gt than in WT (23.1±1.3ms vs. 21.7±1.3ms; p=0.002). Functional testing revealed an electro-anatomical refractory period in CAP2gt/gt (51.3±4.6 ms vs. 47.5±1.2 ms, p=0.01). The ventricular refractory period (VRP) was slightly prolonged in CAP2gt/gt (36.7±5.8ms) compared to WT (35.7±5.2ms; p=0.03). The probability of induction of ventricular tachycardias (VTs) was significantly raised in CAP2gt/gt (16% vs. 5% in WT; p=0.01). Interestingly, in CAP2gt/gt the probability of induction of VTs (7%) was as low as in WT. The inducibility of atrial fibrillation (AF) did not differ among the groups. Conclusions: Loss of CAP2 results in marked changes in heart rate, atrial and ventricular conduction times and refractory periods. This points towards a significant involvement of CAP2 in a normal sinus node function as well as a normal conduction system. CAP2gt/gt leads to increased conduction delays and the lack of further increase in the incidence of VTs in CAP2gt/gt may originate from a further prolongation of VRP with antiarrhythmic effects. Cases of right ventricular cardiomyopathy with no real cause of an underlying disease may be due to dysfunction of CAP2, so further evaluation of its influence on cardiomyopathy and arrhythmogenesis should ensue to fully understand its functioning.

### NRDc regulates circulatory dynamics through modulating sinus node automaticity and cardiac sympathetic innervation

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We identified nardilysin (NRDc), a zinc peptide of the M16 family as a specific binding partner of b-H-EGF, and demonstrated that NRDc enhances ectodomain shedding of multiple membrane proteins through activation of ADAM. To explore the physiological functions of NRDc, we generated NRDc-deficient mice (Nrd1−/−) and found that NRDc regulates axonal maturation and myelination in the CNS and the PNS through mediating neurite growth. The role of NRDc in the cardiovascular system, however, has not been clarified.

Nrd1−/− showed hypoplastic heart and severe Bradycardia compared with Nrd+/+ (HR:Nrd+/+ vs. Nrd1−/−: 719±44 vs. 579±44/min, p<0.001). ECG monitoring by telemetry system demonstrated the remarkable bradyarrhythmia of Nrd1−/− throughout the day. Pharmacological blocking of autonomic nervous system by the simultaneous treatment with metoprolol and atropine showed that the intrinsic heart rate of Nrd1−/− is significantly lower than that of Nrd+/+. Quantitative PCR showed that the mRNA level of HCN4 in Nrd1−/− heart, which is essential for the sinus node automaticity, was significantly lower than that of Nrd+/+ heart, which occurred remote from the site of ACO-application. The mean of epicardial coupling intervals of breakthroughs and dominant interval at the site of earliest activation did not show R-waves, but just 44% of them could be explained by transmural conduction (contralateral activation within 8ms). Flecainide inhibited ACO-induced rapid focal discharges at the site of ACO-application. After flecainide, AF was not inducible anymore. Summary: Topical application of ACL induced focal discharges and AF-inducibility.
Methods: We used small RNA interference to downregulate DSP specifically in HL-1 cells derived from the AT-1 mouse. The expression and content of Cx43 and Nav1.5 were determined by western blot and flow cytometry. The location and distribution of Cx43 and Nav1.5 were evaluated by immunofluorescent staining and observed under laser scanning confocal microscopy. The function of Cx43 gap junctions were assessed by scrape loading dye transfer (SLDT) and sodium current recorded with the whole-cell and patch clamp technique.

Results: Western blot and flow cytometry experiments showed that the expression of connexin43 and Nav1.5 were decreased following DSP silencing. Immunofluorescent studies demonstrated that loss of DSP expression led to an abnormal distribution of connexin43 and Nav1.5. SLDT found a decrease in dye transfer across gap junctions in DSP siRNA treated cells. Furthermore, a decrease in peak current density, a shift in voltage dependence of steady-state inactivation, and a prolongation of time-dependence of recovery from inactivation of sodium current were observed in DSP silenced cells.

Conclusion: This is the first demonstration of association between three components of the intercalated disc: DSP, gap junctions Cx43, and the voltage-gated sodium channel Nav1.5 complex. It indicates that impaired mechanical coupling largely affects electrical synchrony, partially explaining the pathogenesis of ARVC.

P4702 Validation of an increased Tpeak-Tend interval in a large series of Brugada syndrome patients as a highly independently ECG parameter related to symptoms and cardiac events

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Introduction: Risk stratification in Brugada syndrome (BS) remains largely debated. Transmural dispersion of repolarisation is a promising new ECG marker linked to sudden death (SD) in BS in a few recent works including a limited number of patients. We study the predictive value of T peak to T end interval (Tp-Te) as surrogate for transmural dispersion of repolarisation in a large cohort of BS patients.

Methods: ECGs from 325 BS patients (259 men, 46±13 yo) were reviewed. Base-line ECG (n=123) or ECG after provocative test (n=202) showing the BS pattern with the highest S:Te voltage were selected in each patient. Tp-Te were measured in each lead at the 12-lead surface ECG and compared between asymptomatic pts and pts with syncope or with SD and/or appropriate ICD therapy (AT).

Results: 228 pts were asymptomatic (70%), 71 presented with unexplained syncope and 24 with SD. In each lead of the 12-lead surface ECG and compared between asymptomatic pts and pts with syncope or with SD and/or appropriate ICD therapy (AT).

Conclusion: Marked transmural dispersion of repolarisation such as Tp-Te in preclinical leads are highly related to symptoms and major arrhythmogenic events in BS. This simple ECG parameter could be used for further risk stratification.

P4704 Ranolazine suppresses atrial fibrillation in an experimental model of chronic heart failure due to development of atrial postrepolarization refractoriness and slowing of conduction velocity

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Background: In a recent study, ranolazine (RAN) was reported to be effective and safe in converting atrial fibrillation (AF) to sinus rhythm by intake of a single dose ("pill in the pocket") in patients with structural cardiac abnormalities. The apparent electrophysiologic safety and the ability to use it in patients where other Na+ channel blockers are contraindicated could have enormous economic implications.

Methods and results: In 7 female rabbits CHF was induced by 4 weeks of rapid ventricular pacing leading to a significant decrease in ejection fraction. 12 rabbits were sham-operated and served as controls. Isolated failing and sham hearts were perfused using the Langendorff method and were paced with cycle lengths from 350 to 150ms in the atrium. In addition, burst pacing was used to induce atrial fibrillation. Two monophasic action potential recordings on the left- and right-epicardium showed an increase of atrial action potential duration (aAPD) and effective refractory period (aERP) in CHF hearts as compared with controls. Additional infusion of acetycholine (1μM) and isoproterenol (1μM) led to AF in all failing and in 11 sham hearts. Simultaneous infusion of RAN (10μM) suppressed AF in 55% of sham- and 57% of failing hearts. RAN had no effect on aERP but led to a significant increase of aERP (sham: <28ms; CHF: >24ms) leading to marked increase of atrial postrepolarization refractoriness (αPRR), defined as the difference of aERP and aAPD. RAN application significantly increased conduction velocity in sham (+14ms) and failing (+16ms) hearts, respectively.

Conclusion: In the present study, administration of RAN has been shown to be effective in suppressing AF not only in sham- but also in failing hearts. The antiarrhythmic effect is due to development of αPRR and a marked effect on conduction velocity. RAN might be a new safe option to reduce the burden of AF in CHF, where other antiarrhythmic drugs are contraindicated. The described electrophysiological mechanism should be adopted as a fascinating novel antiarrhythmic option in heart failure.

P4705 Myofibroblasts do not contribute to the substrate for atrial fibrillation. A study of human left atrial appendages

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Purpose: The contribution of myofibroblasts to the substrate of atrial fibrillation (AF) is unknown. The electrical correlates between myocytes and myofibroblasts may promote arrhythmogenicity through a decrease of conduction velocity (CV). Ablation of myofibroblasts with Latrunculin-B (LatB) in cell cultures of myocytes and myofibroblasts reverses these changes. We hypothesized that myofibroblasts

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Cervical vagal nerves contain sympathetic ganglion cells and sympathetic nerve fibers in addition to parasympathetic nerve fibers. Cervical VNS may achieve its therapeutic effects by activating both branches of the autonomic nervous system.

**Methods:** The LAA of patients undergoing thoracoscopic surgery for AF was excised. The LAA preparation was superfused with Tyrode’s solution in a tissue bath and optical mapping was performed with d-4-ANEPSS. The LAA was paced at 100 bpm and exposed to LatB for 1 hour and CV was measured every 5 minutes. Immunohistochemical staining for alpha-SMA and connexin 40 was performed to identify myofibroblast in tissue preparations and differentiate myofibroblast from vascular smooth muscle cells.

**Results:** A total of 21 LAAVs were studied (0.1 and 1 micromol LatB and control, 7 per group). No spontaneous activity was observed. Longitudinal CV was 0.27-1.43 mm/ms and transversal CV was 0.04-1.11 mm/ms. LatB did not affect CV irrespective of the type of AF. Run down of the model, characterized by a reduction in CV in time, was observed. Concordantly with the outcome of the electrophysiological experiments, myofibroblasts were not detected with immunohistochemical staining of LAA.

**Conclusion:** Exposure of human LAA preparations to LatB does not change CV. Furthermore, immunohistochemical staining does not reveal the presence of myofibroblasts in LAA of AF patients. These data suggest that myofibroblasts do not play a major role in the pathophysiological substrate of human AF.
The anatomic relationship between the right and left ventricular outflow tracts: its relevance in catheter ablation

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Purpose: Premature ventricular contractions, ventricular tachycardia and initiating beats for ventricular fibrillation have all been localized at the level of the right and left ventricular outflow tracts (RVOT and LVOT). Catheter ablation at and around the junction between the outflow tracts and the great arteries is being increasingly performed. Detailed anatomic information of these structures may be useful to perform the ablation techniques in a safer and more efficient way.

Methods: Fifteen structurally normal human hearts (10m, 47±5 years) were carefully studied by sagittal and horizontal histological sections. The junction between the LVOT and RVOT were serially sectioned at 10-μm thickness, and stained by Goldner and Masson trichrom an oath 88. By light microscope, the minimal distance between the endocardium of the LVOT and the endocardium of the RVOT, at the level of the supraventricular crest, was measured using image analysis software.

Results: The RVOT is a muscular structure of variable length (range 13-24 mm) that supports the semilunar leaflets of the pulmonary valve. Its posterior and inferior borders of a prominent muscular crest, called supraventricular crest that separates the inflow and outflow components of the RV. The supraventricular crest is in contact with the posterior part of the LVOT, as it inserts in the interventricular septum. The minimal distance between the endocardium of the right and left ventricles was 7.5 mm (range 4-14 mm) being in 3 hearts (20%) greater than 10 mm.

Figure 1. RVOT/LVOT anatomic relationship

Conclusions: The myocardial thickness at the level of the RVOT and LVOT may be greater than 10 mm. An endocardial ablation approach of idiopathic outflow tract tachycardias cannot be performed due to this anatomic finding, suggesting the need of an epicardial approach in selected cases.

Acute block of Kv1.5 channels by DHA increases atrial refractory period

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Kv1.5 is considered to be a potential molecular target for treatment of atrial fibrillation or flutter. Polynaturated fatty acids such as docosahexaenoic (DHA) and eicosapentaenoic acids could exert anti-arrhythmic activity in animal models as well as in human. Thus by means of patch clamp technique we investigated a potential regulation by DHA on Kv1.5 channels stably transfected in HEK 293 cells. Among, mono-unsaturated and saturated fatty acids, DHA was found to gate Kv1.5 channels. For a simple channel open mechanism the most powerful inhibition of IKv1.5 that appears to be sufficient to significantly increase AERP in anesthetized rabbit. Such a lengthening of AERP may be of therapeutic benefit in atrial fibrillation.

Depletion of connexin45 and connexin30.2 deteriorates AV-nodal conduction in the murine heart

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Introduction: Connexin (Cx) 30.2 provides physiological conduction slowing in the murine AV-node. Cx45 has been proposed to maintain basal AV-nodal conduction. The interaction of the predominant connexins Cx45 and Cx30.2 in the murine AV-node has not yet been systematically evaluated. Deletion of Cx45 deficient mice are embryonic lethal.

Methods: We interbred a transgenic mouse line cardiacaly depleted for Cx45 mice (Cx45–/–) with Cx30.2 knock out (KO) mice (Cx30.2–/–), resulting in Cx45–/–Cx30.2–/– double KO offspring. In these and control wildtype (WT) littermates, we performed transvenous catheterization to assess standard EPI-parameters (n=14).

Results: Baseline conduction was impaired in Cx45–/–Cx30.2–/– mice. PQ-intervals were significantly prolonged in the Holter ECG recordings of Cx45–/– versus WT littermates (41.0±2.2 ms vs. 36.3±1.3 ms, p<0.05). When Cx30.2 was additionally deleted in Cx45–/–Cx30.2–/–, PQ was more prolonged as compared to Cx45–/– (43.5±1.6 ms vs. 41.0±2.2 ms, p<0.05). In vivo ECG showed prolongation of the A-His interval as surrogate of supra Hisian conduction disturbances in Cx45–/– versus WT (33.3±5.3 ms vs. 26.9±2.1 ms, p<0.05), which was more pronounced in the double KO versus WT littermates (48.3±4.6 ms vs. 33.3±5.3 ms, p<0.02). AVNRP was shortened in the double KO. Spontaneous AV-blocks did not occur in none of the genotypes. Inducibility of atrial and ventricular arrhythmias was equal among the groups.

Conclusions: Our data show prolonged AV-intervals and impaired AV-nodal conduction under fast heart rates in mice with conditional cardiac deletion of Cx45. These findings support the thesis of Cx45 as a provider of basal AV-nodal conduction. When Cx30.2 is additionally missing, AV-nodal conduction is more severely impaired as in the Cx45 single knock out. These results prove that predominantly expressed Cx45 and Cx30.2 are crucial for maintaining AV-nodal conductivity.
Dexmedetomidine and clonidine inhibit ventricular tachyarrhythmias in a rabbit model of acquired long QT syndrome

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Purpose: We hypothesized that alpha-2 AR agonists have an inhibitory effect on abnormal repolarization-related ventricular tachyarrhythmias (VTs).

Methods: Effects of dexmedetomidine and clonidine on the occurrence of VTs were assessed in a methoxamine-sensitized rabbit model of acquires long QT syndrome (n=45). To verify that VTs in this animal model were triggered by abnormal early afterdepolarization (EAD), monoschig action potential on the left ventricular surface was recorded in 28 open-chest rabbits.

Results: Incidence of VT significantly decreased during the treatment with dexmedetomidine (1 μg/kg/min; 5/12 (p<0.01 vs. control)) or with clonidine (33.3 μg/kg/min; 10/18 (p<0.01)), as compared with that in control rabbits (14/15). EAD-like hump was less frequently detected during DNA screw with clonidine or dexmedetomidine (2/14) than in saline-treated rabbits (9/10, p<0.005). Presence of hump was significantly related with the advent of VTs (p<0.05).

Conclusion: Alpha-2 AR agonists have an inhibitory effect on VTs in the rabbit long QT model.

Lymphocytic cell infiltration of myocardium is associated with the episode of ventricular fibrillation in patients with Brugada syndrome

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Purpose: Brugada syndrome is a disease known to cause ventricular fibrillation (VF) with a structurally normal heart and is linked to SCN5A gene mutation. The existence of myocarditis on endomyocardial biopsy samples in patients with Brugada syndrome is still debated. The aim of the present study was to investigate by endomyocardial biopsy whether the presence of lymphocytic cell infiltration on myocardium and its association with clinical features in patients with Brugada syndrome.

Methods: We studied consecutive 73 patients (71 males; mean age 48±11 years) with Brugada syndrome. All patients underwent cardiac ultrasonography, coronary and ventricular angiography, endomyocardial biopsy from right ventricular septum, electrophysiological (EP) study, and DNA screening of the SCN5A gene. The lymphocytic cell infiltration of myocardium was determined by the presence of inflammatory cell infiltration by CD45RO immunohistochemical staining associated with necrosis or degeneration of adjacent myocytes in high power field image.

Results: SCN5A mutation was detected in 15 patients. VF episode was detected in 17 patients. Lymphocytic cell infiltration of myocardium was detected in 7 patients (2 patients with SCN5A mutation and 5 without SCN5A mutation) out of all patients and was detected in 4 patients out of 17 patients with episode of VF. The existence of lymphocytic cell infiltration was associated with the VF episode in patients with Brugada syndrome (P=0.047), but not with SCN5A mutation, syncpe, family history, or VF induction in EP study.

Conclusion: Lymphocytic cell infiltration was detected in patients with Brugada syndrome in both of SCN5A positive and negative group. And the existence of lymphocytic cell infiltration is associated with VF episode in patients with Brugada syndrome.
Effects of renal sympathetic denervation on heart rate and atrioventricular conduction in patients with resistant hypertension

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Background: Renal sympathetic denervation (RDN) reduces sympathetic activity and blood pressure (BP) in patients with resistant hypertension. The present study was aimed to investigate the effects of RDN on HR and other electrophysiological parameters.

Methods: 136 patients aged 62.2 ± 0.8 years (58% male, BP 177.2 ± 29.3/1.1 mm Hg) with resistant hypertension underwent RDN. BP and a 12-lead electrocardiogram (ECG) were recorded before, 3 months (n=122), and 6 months (n=84) after RDN.

Results: After 3 months (3M) and 6 months (6M), systolic BP was reduced by 25.5 ± 2.4 mm Hg (p = 0.001) and 28.1 ± 3.3 mm Hg (p = 0.001). HR at baseline was 66.1 ± 1.1 beats per minute (bpm) and was reduced by 2.6 ± 0.8 bpm after 3 months (p = 0.001) and 2.1 ± 1.1 bpm after 6 months (p = 0.046). Change of HR correlated with HR at baseline: patients with HR at baseline between 60-71 bpm and ≥71 bpm had a reduction of 2.9 ± 7.6 bpm (p = 0.008) and 9.0 ± 8.6 bpm (p < 0.001), respectively, whereas in patients with baseline HR > 70 bpm HR increased after 6 months (2.8 ± 8.4 bpm; p = 0.035). Neither baseline HR nor change of HR correlated with changes of systolic BP. The PR interval was < 10 ms at baseline in 21.4 ± 6.7% of patients. A prolonged heart rate corrected QT peak (QTpc) of lead I carried the highest risk of cardiac death in these patients. The primary endpoints were cardiac death and cardiac death from any cause. A prolonged heart rate corrected QT peak (QTpc) of lead I carried the highest risk of cardiac death in these patients.

Conclusion: RDN significantly reduced heart rate and PR interval, as indicators of cardiac autonomic activity, in patients with resistant hypertension. The changes did not correlate to BP reduction.

Distribution of J waves on 87-lead body surface map in patients with inferolateral early repolarization syndrome

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Purpose: J waves in the inferior lead reportedly relate to poor prognosis in patients with inferolateral early repolarization syndrome (ERS). However, little is known about the body surface distribution of J waves and the significance of J waves in ECG leads with ST segment elevation. Present data allow for a new ECG criteria for the differential diagnosis between acute pericarditis and acute coronary artery occlusion.

Methods: This study consists of 15 patients (13 males, mean age 33.6 ± 9.5 years) with ERS and a prior VF who underwent multiple recordings of 12-lead electrocardiogram (ECG) and 87-lead body surface map (BSM) during sinus rhythm. Locations of J waves on ECG were compared with distributions of J waves on the body surface and the clinical characteristics of patients. J wave was defined as an elevation of at least 1 mm (0.1 mV) of the J point in at least 2 leads, either as QRS slurring or notching in the inferior lead (II, III, aVF), lateral lead (V4–V6), and high lateral lead (I, AVL) followed by ST elevation. Type 1 Brugada syndrome was excluded from this study.

Results: J waves were noticed on extensive body surface area, not only in the lower anterior chest but also in the lower back where the excitation of left ventricle is reflected in 9 patients with inferior J waves. In contrast, they were noted in the restricted area of left mid lateral chest in 11 patients with lateral J waves, and in the left upper chest in 5 patients with high lateral J waves. Two patients with J waves in 10 lead had much wider J wave distribution on BSM. During 11.5 ± 4.14 years follow-up, 14 patients received implantable cardioverter-defibrillator and 7 of 15 (47%) patients had recurrences of VF with a rate of 80%, 46%, and 33% in patients with high lateral, lateral, and inferior J waves, respectively.

Conclusion: Patients with J waves in the inferior or global leads on ECG exhibited a wider distribution of J waves on the body surface, although high lateral J waves tended to link with poor outcome in ERS patients with Vf.

Is QRS axis pattern associated to the type of surgical repair in adults with operated tetralogy of fallot?

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Introduction: Until the development of the transatrial-transpulmonary approach, surgical repair of Tetralogy of Fallot (ToF) was achieved through a right ventriculotomy causing right ventricular (RV) conduction disturbance. We studied QRS
Early repolarization patterns in young healthy individuals: prevalence, morphological characteristics and impact of gender, ethnicity and physical activity

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Purpose: Early repolarization (ER) is commonly observed in athletes and young healthy individuals. Recently, ER in the inferior and lateral leads has been associated with sudden cardiac arrest from idiopathic ventricular fibrillation. We studied the prevalence, distribution and morphology of ER patterns in inferior and lateral leads in young healthy individuals.

Methods: 12-lead electrocardiogram (ECG) was performed at rest in 1929 young healthy individuals (age range 13-38 years) between February and September 2011. We evaluated the impact of gender, ethnicity and physical activity on ER. Individuals were divided into physically-active (exercise >2 hours/week) and sedentary. Early repolarization was defined as notched or slurred J-point elevation of at least 0.1 mV from baseline, in ≥2 contiguous inferior or lateral leads; anterior ER patterns were not considered in this study. The morphology of ST-segment was classified as rapidly ascending/up sloping or horizontal/descending.

Results: The mean age of participants was 17.9±4.4 years, of which 1406 (73%) were male, 1557 (80%) were physically active and 1780 (82%) were Caucasians. ER pattern in inferior and lateral leads was present in a total of 382 (19.8%) cases; of these 40% were in the inferior leads, 35% in lateral leads and 25% in both. Notched ER pattern was more prevalent compared to slurred morphology, and more commonly associated with ascending/up sloping ST-segment elevation. ER was significantly more prevalent in males compared to females (20% vs. 12%, p<0.003), in physically-active people compared to sedentary (20.4% vs. 14.8%, p<0.013), and in Afro-Caribbean compared to Caucasians (31.2% vs. 19.9%, p=0.012). In addition, voltage criteria for left ventricular hypertrophy and sinus bradycardia were a common associated finding in individuals with ER pattern compared with those without (p<0.0001 and 0.0001 respectively). Only 5% of individuals with ER had J-point elevation of >0.5 mV.

Conclusion: Early repolarization is a common finding in young healthy individuals, and is more prevalent in males, physically-active individuals and those with Afro-Caribbean ethnicity. The inferior leads were more commonly involved but the difference was not statistically significant. Notched ER pattern with ascending ST-segment elevation was the most commonly observed morphological pattern. More research is required to understand precise long term implications of such repolarization changes in young individuals.
Screening for arrhythmogenic myocardial substrate by 12-lead ECG, high resolution ECG and T-wave alternans in patients with low to intermediate sudden cardiac death risk

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Aims: Increased QRS score, wide spatial QRS-T angle, T-wave alternans (TWA), and late potentials by signal averaged electrocardiogram (SAECG) are independent predictors of cardiovascular mortality in the general population. We analyzed whether these electrocardiographic (ECG) parameters enable screening of patients for myocardial scar features implicated in sudden cardiac death risk.

Methods and results: We screened a 6-month period of the entire 12-lead ECG database of Johns Hopkins Hospital and identified 800 patients age >70 years from non-critical care areas and no record of reduced life expectancy who had QRS (130 ms) and/or spatial QRS-T angle >10°, as well as left ventricular ejection fraction (LVEF) ≤35%. All individuals were invited to participate, of whom 77 enrolled in the study and underwent clinical examination, SAECG, 30-minute ambulatory ECG recording for TWA, and total late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) study to determine scar presence and pattern as well as to characterize gray zone, core, and total scar size.

The mean age was 60 ± 10 years, with 70% males and no known heart disease in 43% of the study population. Patients’ mean LVEF was 58 ± 8%. Previously unreported myocardial scar was present in 41 (53%) patients, of whom 19 (48%) exhibited a typical ischemic pattern. Median and inter-quartile range for scar, core scar, and gray zone extent were 8% [4; 19%], 5% [3; 8%], and 2% [1; 7%] of left ventricle (LV), respectively. QRS-T angle but not QRS score was associated with the presence of scar and ischemic scar pattern: QRS score was related to total scar size and gray zone size (R² = 0.13, P = 0.02; R² = 0.12, P = 0.005, respectively). There was a significant independent association between TWA level with total scar size (R² = 0.18; P = 0.001) and gray zone size (R² = 0.10; P = 0.002, respectively). There was a significant independent association between TWA level with total scar size (R² = 0.18; P = 0.001) and gray zone size (R² = 0.10; P = 0.002, respectively). There was a significant independent association between TWA level with total scar size (R² = 0.18; P = 0.001) and gray zone size (R² = 0.10; P = 0.002, respectively). There was a significant independent association between TWA level with total scar size (R² = 0.18; P = 0.001) and gray zone size (R² = 0.10; P = 0.002, respectively).

Conclusions: ECG screening by QRS score >5, QRS-T angle >10°, and TWA identifies patients with preserved LVEF but previously unreported myocardial scar with arrhythmogenic potential.

Prevalence, electrocardiographic characteristics and variations of early repolarization syndrome on a population of healthy subjects

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Background: Infero-lateral repolarization has been considered benign for a long time, however recent studies have demonstrated a possible association with sudden death.

Methods: Electrocardiographic (ECG) records of 1983 patients undergoing routine medical examination at the Principal Centre of Medical Expertise of Flight Crew for french Army from early January to early March 2000 were described. Early repolarization was defined as an elevation of J wave of at least 0.1 mv in the inferior and lateral leads. In patients with early repolarization, retrospective analysis of electrocardiograms from the following ten years (2000-2010) was carried out. Clinical and electrocardiographical characteristics were statistically analyzed.

Results: The prevalence of early repolarization was estimated at 5.7% (CI 95%, 4.7-6.7%). 3 patients presented with ECG severity criteria (interlateral early repolarization, J wave ≥ 0.2 mv and notch). For 20% of patients early repolarization was intermittent and 56.5% had substantial variations in J wave amplitude, morphology or territory. Early repolarization was commonly associated with ST-segment elevation, prominent T waves, slower cardiac heart rate and shorter corrected QT duration. No malignant ventricular arrhythmia nor sudden death occurred among the 3 patients presenting with ECG severity criteria during the 10 years follow-up.

Conclusions: Our data are consistent with previous studies concerning early repolarization syndrome. Given the high prevalence and important fluctuations of early repolarization, every patient who presents with this syndrome cannot be considered to be at risk of sudden death. Further research is needed to identify the electrocardiographic forms of this syndrome which are associated with an increased risk of mortality.
in Eastern Europe. Several studies have investigated the effect of seasonality and sudden cardiac death (SCD). Less commonly investigated is the short-term effects of change in ambient temperature and SCD. We investigated the association between hourly and mean daily change in ambient temperature and SCD.

**Methods:** We evaluated the effect of ambient temperature and the risk of SCD, comparing data from the Heart Start registry with local hourly measurements of atmospheric temperature in Scotland from January 1995 to December 2004, using a case-crossover design.

**Results:** 29,954 victims suffered a SCD in the studied time frame. Across all distances and all time lags, there was an increase in risk of SCD with lowering of ambient temperature. There was a 7.6% (95% CI 2.7% - 12.3%) increase in the risk of SCD per 10 degree lowering of the ambient temperature. The association with temperature remained up to 24 hours (Lag 0-1 days) prior to the SCD with sensitivity analysis showing patients <65 years and those with known heart disease (Figure 1) being more vulnerable.

**Conclusion:** In this national comprehensive registry, SCD was strongly correlated with a lowering of the ambient temperature at lag 0 hours up to lag 0-1 days suggestive of a much more acute mechanistic link. This study has major public health implications in measuring risk of SCD in vulnerable patients by the provision of targeted advice or other interventions.

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**P4731 How to differentiate patients at risk of cardiac and non-cardiac death using heart rate and its variability?**

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Patients with left ventricular ejection fraction (LVEF) ≤ 35% are currently treated with implantable cardioverter-defibrillator (ICD) in primary prevention. However, those who exhibit high non-cardiac risk will probably not benefit from ICD. Heart rate variability (HRV) and average heart rate (HR) are risk factors for both cardiac and non-cause mortality. HR and HRV are inversely dependent on each other, and mathematical modifications one may strengthen or weaken the HR/HRV dependence.

**Purpose:** To explore if modifications of the HR/HRV dependence enable to differentiate patients at risk of cardiac (CD) and non-cardiac death (NCD) after myocardial infarction (MI).

**Methods:** The study group consisted of 1410 patients with recent MI followed up for 5 years. Seven different classes of spectral HRV indices with increasing HRV/HR dependence were calculated. Their prediction powers were tested by calculation of areas under receiver operator characteristic curves.

**Results:** During the follow-up period, 128 patients died, 71 from cardiac and 57 from non-cardiac causes. As HRV was getting more dependent on HR, its predictive power progressively increased for CD but decreased for NCD. Of all spectral indices, a modified very low frequency component (VLF), which did not depend on HR, had a high predictive power for NCD. Another modified very low frequency component (VLF7), which highly depended on HR, had a good predictive power for CD. In the multivariate analysis, VLF1 independently predicted NCD (hazard ratio: 5.1, 95% CI: 3.0-8.9) together with VLF4 (HR: 2.6, 95% CI: 1.4-5.0) and age ≥ 65 years (HR: 2.4, 95% CI: 1.4-4.1); whereas VLF7 predicted CD (HR: 3.7, 95% CI: 1.9-7.2), together with LVEF (≤ 35%), age ≥ 65 years (HR: 2.1, 95% CI: 1.3-3.3), diabetes (HR: 2.0, 95% CI: 1.2-3.3) and arrhythmia signs on Holter (i.e. > 10 ventricular premature complexes/h and/or non-sustained ventricular tachycardia) (HR: 1.9, 95% CI: 1.1-3.1). In patients with VLF4 (≤ 35%), VLF7 was especially effective in anticipating NCD (76% sensitivity, 82.8% specificity), whereas VLF7 predicted CD with 34.5% sensitivity and 91.9% specificity. The combination of VLF1 and VLF7 enabled to select patients at high risk of NCD and low risk of CD among those with VLF4 (≤ 35%) - i.e. the subgroup which would probably not benefit from ICD.

**Conclusions:** By strengthening or weakening the HR/HRV dependence one can get HRV indices which provide distinct information on cardiac and non-cardiac risk of NCD and low risk of CD among those with LVEF ≤ 35%; i.e. the subgroup which would probably not benefit from ICD.

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**P4732 Treatment of patients with inappropriate sinus node tachycardia: if-channel inhibition or ablation?**

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Inappropriate sinus node tachycardia (IST) is a relative rare clinical syndrome defined as increased sinus rate at rest, and/or inadequate response to physical or emotional stress without any underlying disease. In the last years 25 patients (23 women, 2 men; age: 18-57 (33) years) were treated with IST due to palpitations. Patients had no structural heart disease (EF: 65±2%), TSH values were within normal limits, but resting heart rate were repeatedly high: 106±3/min. The results of Holter recording (expressed as minute-maximum and average heart rate/min) without medication showed high heart rate values: 58±2-163±3 (96±2) min. The bicycle ergometry showed an average loading capacity of 120-35W (heart rate: control (C): 104±6/min, top (T): 170±6/min). The aim of the study was to evaluate the efficacy and safety of a selective sinus node If channel inhibitor drug, the ivabradine in the IST patient group. The ivabradine therapy decreased the heart rate significantly and dose-dependently compared to the control values: ivabradine: 2x5 mg/day: 50±2-131±5 (-76±2/min (p<0.001), ivabradine 2x7.5 mg/day: 48±1-130±6 (-72±2/min (p<0.001), and decreased the heart rate during ergometry: ivabradine: 2x5 mg/day: 83±4% (p<0.001), 2x7.5 mg/day: 77±4; 13% (p<0.001). The loading capacity improved but did not change significantly (135±6W, ns). The ivabradine treatment was well tolerated, there was no sinus bradyarrhythmia episode. All patients experienced symptom relief, three patient suffered from phosphenes, which completely resolved in a few days. Based on our clinical experiences IST can be treated with the sinoatrial node modulator drug ivabradine successfully and safely. Ivabradine significantly decreased, improved heart rate frequency spectrum and
The role of non-invasive methods in determining the arrhythmic risk in myotonic dystrophy type 1

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Purpose: In myotonic dystrophy type 1 (MD1) the risk of cardiac death is higher than in the general population and atrial or ventricular arrhythmias are frequent. The aim of this study was to assess the determinants of arrhythmic risk in patients with MD1 using non-invasive methods.

Methods: Eighty-four patients (62% males; age 41±15 years) with a clinical-genetic diagnosis of MD1 (class E1=11%; E2=75%; E3=14%) were enrolled. All patients underwent cardiological evaluation, 12-lead ECG, echocardiography, 24-hour ECG/Holter with heart rate variability (HRV) and neurological assessment at entry. During a mean follow-up of 46±28 months (±2 visits echo-ECG-Holter data and arrhythmic events were collected.

Results: During the follow up 8 patients (9%, incidence 2/100-year) died (age at death 48±11 years). Six (75%) of the deaths were cardiac: 2 cardiac deaths (SD), 1 aborted SD i.e. ICD shock on ventricular fibrillation (VF), and 3 deaths due to heart failure. Four patients (5%) developed major arrhythmic events (SD/aborted SD, VF, sustained or non-sustained ventricular tachycardia), and 7 patients (8%) atrial flutter/fibrillation (AF). According to current guidelines, 7 patients received pacemaker and 6 ICD. The incidence of cardiac death was associated with prolonged PR and QRS intervals at baseline ECG (244±48 msec vs. 189±34, p=0.003 and 126±23 msec vs 96±21, p=0.002 respectively), with presence of AF (50% vs 11%, p=0.009) at baseline or during follow up, with lower SDNN (100±34 vs 221±53, p=0.06) and SDANN (81±15 vs. 132±41, p=0.04) values at HRV. Patients who developed major arrhythmic events had a trend toward a longer QRS duration at baseline ECG (118±31 msec vs 97±23, p=0.07) and more frequent premature ventricular beats/PVBs at ECG-Holter (2652±1578 vs 490±1578, p=0.018). Patients who developed AF were characterized by older age (51±17 years vs 39±14, p=0.047), longer PR interval at baseline ECG (257±49 msec vs. 198±32, p=0.03), and higher HRV (RR mean 968±217 vs. 837±84, p=0.008; SDNN 76±45 vs 139±39, p=0.04; RMSSD 89±53 vs 43±21, p=0.001).

Conclusions: In MD1 patients cardiac-deaths are associated with conduction disturbances at baseline ECG, presence of AF and HRV data suggesting increased sympathetic activation. Major arrhythmic events are associated with intraventricular disturbances at ECG and frequent PVBs at Holter. Atrial fibrillation is more frequent in patients with baseline atrio-ventricular conduction disturbances and vagal prevalence. Non-invasive cardiologic evaluation is important for arrhythmic risk assessment, identifying patients who can develop major tachyarrhythmic events.

The importance of atrioventricular conduction and myocardial function in ventricular arrhythmogenesis in lamin A/C mutation carriers

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Purpose: Mutations in the Lamin A/C gene may cause dilated cardiomyopathy (DCM), typically accompanied by atrioventricular block (AVB) and high risk of ventricular tachycardia (VT). VT may occur before development of DCM and risk stratification is challenging. Mechanisms of arrhythmias in these patients are not fully understood.

Methods: We included 41 Lamin A/C mutation carriers. PQ interval from resting ECG and occurrence of VT were recorded. Myocardial function was assessed by echocardiography as ejection fraction (EF) and by speckle tracking strain from 16 LV segments as global longitudinal strain. Regional function in the interventricular septum was assessed by averaging strain from 4 septal segments and defined as septal strain.

Results: VT was documented in 21 patients (51%). Importantly, 13 patients without evident DCM had VT (62%). Prolonged PQ interval (p<0.001), presence of AVB (p<0.001) and reduced global longitudinal strain (p=0.01) were markers of VT, while EF was not (p=0.53). By ROC analysis, PQ interval >230 ms showed the best ability to discriminate between those with and without VT with a sensitivity and specificity of both 87%. PQ interval was an independent predictor of VT in multivariable analysis (OR=1.35, p=0.01). Septal strain was markedly reduced compared to the rest of LV segments (-16.7% vs. -18.7%, p<0.001). Prolonged PQ interval correlated with reduced septal function (R=0.41, p=0.03).

Electrocardiogram/non invasive studies/syncope

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Conclusion: Prolonged PQ interval was the best predictor of VT and may help arrhythmic risk stratification in Lamin A/C mutation carriers. Myocardial function was most decreased in the septum and correlated to prolonged PQ interval. These findings indicate that reduced septal function and AVB are involved in mechanisms of ventricular arrhythmias in Lamin A/C mutation carriers.

Clinical aspects and prognosis of type 1 ECG pattern of Brugada syndrome

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Purpose: This study investigated the clinical aspects and long-term prognosis of type 1 ECG pattern of Brugada syndrome (BS).

Methods: The clinical data of 68 apparently healthy individuals (55 males, age 44.7 ± 12.7 years) with spontaneous (n=27) or drug-induced (n=41) type 1 ECG pattern of BS were retrospectively analyzed.

Results: Twenty-eight subjects were symptomatic with a history of syncope (41.2%), and 18 displayed a positive family history of BS and/or sudden cardiac death (36.5%). Electrophysiologic study was performed in 37 subjects, and programmed right ventricular stimulation induced ventricular tachycardia/fibrillation in 25 of them (67.5%). A cardioverter defibrillator (ICD) was implanted in 27 individuals (39.7%). During a mean follow-up period of 5.0±3.57 years, five symptomatic subjects suffered appropriate ICD discharges due to ventricular arrhythmias (7.4%, 1.7% per year in total population, 3.55% per year in symptomatic individuals), and one died due to non-cardiac causes. None of the asymptomatic individuals had syncope or ICD therapies. A history of syncope (p: 0.005) as well as a prolonged QRS duration in leads II (p: 0.026) and V2 (p: 0.001) were significantly associated with ventricular arrhythmic events during follow-up. Sinus node dysfunction and atrial arrhythmias were observed in 8.8% and 20.6% of subjects, respectively.

Conclusions: In this study population, the mean arrhythmic event rate per year in symptomatic individuals with BS phenotype was 3.55%. Asymptomatic subjects with type 1 ECG pattern of BS display a benign clinical course.

T-wave alternans is helpful for predicting recurrence of fatal arrhythmias in ventricular fibrillation survivors

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Backgrounds: T-wave alternans (TWA) is useful for predicting the occurrence of ventricular tachyarrhythmias in various heart diseases. However, little is known about the clinical significance of TWA measurement in patients with past history of ventricular fibrillation (VF).

Methods: We studied 22 VF survivors (15 males, mean age 58 years) who received implantable cardioverter-defibrillator implantation. The patients of J wave syndrome were excluded from this study. We measured plasma B-type natriuretic peptide (BNP) and assessed left ventricular ejection fraction (LVEF) by echocardiography. Additionally, QRS duration and QTc interval were measured in electrocardiogram. TWA value was calculated by the time-domain moving average method. All subjects were divided into two groups based on whether TWA value was above 65 μV (n=11, Group-A) or not (n=11, Group-B). We compared these parameters and the appearance of ventricular arrhythmias requiring appropriate shock therapy in the observation term (8.8±5.9 months) between two groups.

Results: BNP and LVEF were not different between two groups (BNP, 213±292 pg/ml vs. 175±154 pg/ml; LVEF, 42.4±14.8% vs. 46.6±16.3%). QRS duration and QTc interval were not different between two groups (QRS duration, 121.3±23.2 msec vs. 107.2±16.1 msec; QTc interval, 454.8±12.7 msec vs. 431.6±54.1 msec). However, ventricular arrhythmias requiring appropriate shock therapy occurred more frequently in Group-A than in Group-B (55% vs. 9%, P<0.05). In Kaplan-Meier actuarial curves for arrhythmic event-free rates, Group-A had lower event-free than Group-B (P<0.05).

Conclusions: These results suggest that T-wave alternans is useful for predicting the recurrence of ventricular arrhythmias or adverse outcomes in patients with past history of VF.
Utility of magnetocardiography for detection of delayed potentials, epsilon waves, with arrhythmogenic right ventricular cardiomyopathy

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Purpose: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by hypokinetic areas involving the free wall of the right ventricle, with fibro-fatty replacement of the right ventricular myocardium, with associated arrhythmias originating in the right ventricle. Diagnostic ECG finding includes epsilon wave, which is interpreted as a delayed potential in RV. Some cases are difficult to identify the delayed potentials. The aim of this study was to visualize the delayed potentials and compare the delayed potential point using magnetocardiography (MCG).

Methods: This study included 14 cases with ARVC who were diagnosed by Task Force of WHO/ISH (1996) and biopsy, echocardiography and imaging, they were examined 64-channel MCG waveforms. 64-channel MCG waveforms were examined before electrophysiological study and ablation for ventricular premature contraction or ventricular tachycardia. 6 of them showed typical abnormal potential representing the epsilon wave at the end of QRS complex and right in front of T wave on electrocardiography (ECG). 8 cases were difficult to detect the delayed potentials by 12-leads ECG. A current arrow map (CAM) depicted the propagation of the delayed potentials. The locations of the delayed potentials identified by MCG were compared with ablation successful site tagged on the electroanatomical map.

Results: 6 of 8 (75%) with undetectable delayed potential cases could identify the delayed potentials at the end of QRS complex, using MCG. The origins of the delayed potentials deduced CAM agreed with that from the invasive study in 12 of 14 patients.

Conclusion: Magnetocardiography was useful for detecting the presence of delayed potential, epsilon wave, and estimating delayed potential points before the catheter ablation.

SYNCOPE

Home orthostatic training is not effective in elderly patients With vasovagal syncope - a prospective randomised controlled trial

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Objective: To assess the effect of home orthostatic training (HOT) on autonomic reflexes in elderly patients with vasovagal syncope (VVS).

Design: A single blind randomised control trial.

Setting: Eastbourne District General Hospital, East Sussex NHS Trust.

Interventions: The over 65 group were randomised 1:1 to active HOT (O65+) or sham HOT (O65). The U65 group received active HOT. Participants performed HOT/sham HOT and recorded their training and symptoms. Patients had a repeat tilt test at 3 months.

Main outcome measures: Time to syncope at repeat tilt table testing, low-frequency heart rate variability (LF-HRV), high-frequency HRV (HF-HRV), mean arterial pressure, baroreflex sensitivity (BRS) and mean downstroke BRS were assessed.

Results: Symptomatic benefit occurred in 4 (31%) of the O65+, 4 (29%) of the U65+, and 6 (50%) of the U65. None of the autonomic measures changed significantly in any group (table 1.). 50% of the O65+ group stopped training due to back pain. Time constraint (25%) was the most common reason for cessation in the U65 group.

Conclusions: Despite good tilt training compliance no improvement in autonomic measures in any group was shown. The most common reason for cessation of training was back pain the elderly groups. This study does not support the use of HOT in elderly patients.

Vasovagal syncope mediated by emotional distress associated with increased risk of cardiovascular events

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The aim of the study was to assess whether vasovagal syncope mediated by emotional distress (emotional-VVS) is associated with an increased risk of cardiovascular events (CVEs).

Methods and Results: The study group consisted of consecutive 2248 Cardiology Clinic outpatients aged 61.4 ± 14 years (604 patients with and 1644 patients without CVE), 28.3% of the studied population reported at least one episode of syncope, 8.7% had emotional-VVS. The median age of CVE was 59, the interquartile range 52-66 years. The median time between the first emotional-VVS and CVE was 37 years, interquartile range 26-44 years. The median time between the first emotional-VVS and date of the visit in cardiology outpatient clinic in patients without CVE was 41 years (interquartile range 25-49 years) p<NS. Emotional-VVS was significantly more frequent in patients with CVE than in those without (35% vs 26% p<0.01). For each patient an index date was established. The index date was the one of the first CVE or, in the case of patients without CVE, the date of their visit to the clinic. Survival free of CVE to the index date estimated according to Kaplan-Meier method showed lower probability of survival in patients with emotional-VVS and the survival curves began to drift apart at the age of 50. Multiple Cox regression analysis revealed that shorter CVE free survival was related to male gender, diabetes, an hypercholesterolemia above 240 mg/dl, family history of premature cardiovascular disease (CVD) and positive history regarding the emotional-VVS.

Table. Cox regression survival analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male gender</th>
<th>Smoking</th>
<th>Family history</th>
<th>Diabetes</th>
<th>Total cholesterol</th>
<th>Emotional-VVS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>2.75</td>
<td>2.15</td>
<td>2.15</td>
<td>1.35</td>
<td>1.33</td>
<td>1.68</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>2.25-3.35</td>
<td>1.75-2.66</td>
<td>1.74-2.66</td>
<td>1.04-1.68</td>
<td>1.10-1.59</td>
<td>1.26-2.21</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>&lt;0.005</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>
Two-year diagnostic yield of implantable loop recorders in patients with neurally-mediated syncope enrolled in the ISSUE3 trial

M. Tomiano, M. Brignole, V. Russo, R. Massa, C. Menozzi, M. Gulizia, T. Kus, M. Iorfida, H. H. Ebert, R. Sutton on behalf of ISSUE3 investigators. Ospedale Civile, Bolzano, Italy; del Tiglio Hospital, Department of Cardiology, Lavagna, Italy; S. Annunziata, Taranto, Italy; Ospedale Antonio Eлагo e Casare Arrigo, Alessandria, Italy; Reggio Emilia Hospital, Department of Cardiology, Reggio Emilia, Italy; Garibaldi Nesima, Catania, Italy; Sacred Heart Hospital of Montreal, Montreal, Canada; Molinette, Torino, Italy; Kardiologische Gemeinschaftspraxis, Riene, Germany; St Mary's Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom.

Since the diagnostic yield of implantable loop recorders (ILLRs) is a function of the length of observation, this rate increases by prolonging the observation period. We assessed the diagnostic yield among the 284 patients (pts) enrolled in ISSUE3 trial who completed the 2-year follow-up period. Eligible pts were ≥18 years of age who suffered ≥3 severe syncopal episodes of suspected or certain neurally-mediated syncope (NMS) in the prior 2 years without significant electrocardiographic and cardiac abnormalities. Within 2 years from implantation, 76 pts (27%) had syncopal recurrence with asymptomatic pause ≥3 s (457) or asymptotic pause ≥6 s without syncope (419), 49 pts (17%) had a diagnosis of tachyarrhythmia or syncope due to non-arrhythmic cause and 159 pts (56%) had no diagnosis. No baseline clinical variables (table 1) was able to predict the outcome except a positive history of the last TTT response which was present in 5% of the patients with anic syncope, 51% of those with non-asystolic syncope and in 36% of those without diagnosis (p = 0.003). Clinical characteristics Asystole No asystole No diagnosis p-value

<table>
<thead>
<tr>
<th>Age, mean (SD), y</th>
<th>n=76</th>
<th>n=49</th>
<th>n=159</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 (11)</td>
<td>66 (13)</td>
<td>67 (11)</td>
<td>0.815</td>
<td></td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>37 (49)</td>
<td>22 (45)</td>
<td>66 (42)</td>
<td>0.578</td>
</tr>
<tr>
<td>Syncope events, median (IQR)</td>
<td>6 (1-12)</td>
<td>6 (4-15)</td>
<td>6 (4-10)</td>
<td>0.660</td>
</tr>
<tr>
<td>– Events in the last 2 years, median (IQR)</td>
<td>4 (3-6)</td>
<td>4 (3-7)</td>
<td>4 (3-5)</td>
<td>0.058</td>
</tr>
<tr>
<td>– Events in the last 2 years without prodrome</td>
<td>2 (0-4)</td>
<td>2 (0-4)</td>
<td>3 (1-4)</td>
<td>0.721</td>
</tr>
<tr>
<td>– History of presyncope, n (%)</td>
<td>43 (57)</td>
<td>25 (51)</td>
<td>67 (43)</td>
<td>0.112</td>
</tr>
<tr>
<td>– Hospitalization for syncope, n (%)</td>
<td>45 (59)</td>
<td>30 (61)</td>
<td>78 (50)</td>
<td>0.219</td>
</tr>
<tr>
<td>– Injuries related to fainting, n (%)</td>
<td>1 (1.3)</td>
<td>1 (2.0)</td>
<td>2 (1.3)</td>
<td>0.815</td>
</tr>
<tr>
<td>– Major injuries (fractures, brain concussion)</td>
<td>6 (8)</td>
<td>2 (4)</td>
<td>23 (15)</td>
<td>0.071</td>
</tr>
<tr>
<td>– Minor injuries</td>
<td>30 (40)</td>
<td>16 (33)</td>
<td>64 (44)</td>
<td>0.588</td>
</tr>
<tr>
<td>Tilt test performed, No (%)</td>
<td>65 (86)</td>
<td>45 (92)</td>
<td>142 (90)</td>
<td>0.480</td>
</tr>
<tr>
<td>– Positive of those performed, No. (%)</td>
<td>39 (66)</td>
<td>23 (51)</td>
<td>51 (36)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

In conclusion, about a half of pts receiving an ILR for suspected or certain NMS has been treated within 2 years of observation. Of these, about a half may benefit from pacemaker therapy due to a documented long asystolic pause. The pts with positive response to TTT are more likely to benefit from an ILR strategy.

Incidence, etiology and predictors of adverse outcomes in 43315 patients presenting to the emergency department with syncope: an international meta-analysis

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Background: Syncope remains challenging for Emergency Department (ED) physicians due to difficulties in assessing the risk of future adverse outcomes. While improving our ability to establish the likelihood of the episode and to subsequently guide therapeutic orientation.

Methods: Studies reporting multivariate predictors of adverse outcomes in patients presenting with syncope to the ED were included and pooled, when appropriate, using a random-effect method. Adverse events were defined as ‘incidence of death, or hospitalization and interventional procedures because of arrhythmia, ischemic heart disease or valvular heart disease’.

Results: 11 studies were included. Pooled analysis showed 42% (CI 95%; 32-52) of patients were admitted to hospital. Risk of death was 4.4% (CI 95%; 3.1-5.1) and 1.1% (CI 95%; 0.7-1.5) had a cardiovascular etiology. One third of patients were discharged without a diagnosis, while the most frequent diagnosis was situational, orthostatic or vasovagal syncope in 29% (CI 95%; 12-47). 10.4% (CI 95%; 7.8-16) were diagnosed with heart disease, the most frequent type being bradycardia-tachycardia, 4.8% (CI 95%; 2.2-6.4) and tachyarrhythmia 2.6% (CI 95%; 1.1-3.1). Predictions preceding syncope, e.g. exertional syncope, a history consistent with heart failure, and evidence of bleeding, were the most powerful predictors of an adverse outcome.

Conclusion: Syncope carries a high risk death, mainly related to cardiovascular disease. This large study which has established the most powerful predictors of adverse outcomes, may enable care-related resources to be better focused at high risk patients.

The risk of clotting induced by orthostatic stress patients with vaso-vagal syncope

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Aim of study: Analysis of prevalence of endothelium-dependent clotting and fibrinolysis, as a response to orthostatic stress during head up tilt test (HUTT) in patients with vaso-vagal syncope (VVS).

Study population: 40 pts (15 men, 25 women) aged 18-72 yrs (median of age: 35 yrs. IQR 23.7-55.6) with VVS referred to HUTT. Cardio- and neurogenic reasons of syncope were previously excluded in all pts.

Methods: All pts underwent HUTT acc. to standard Westminster protocol. Before HUTT and at the onset of HUTT provoked syncope blood sample was collected for analysis of clotting and fibrinolysis parameters. We measured: prothrombin time, expressed as international normalized ratio (INR), activated partial thromboplastin time (APTT), serum concentrations of: fibrinogen (FIB) dimer (D-Dimer), tissue plasminogen activator (t-PA) plasminogen activator inhibitor-1 (PAI-1) and von-Willebrand antigen (VWF:Ag) described as % of normal values.

Results: Significant decrease of APTT (30.9 ± 25.6 s; p < 0.0001), INR (1.1 ± 1.03; p = 0.003) and PAI-1 (4.6 ± 3.1 ng/ml; p < 0.001) as well as increase of serum levels of FIB (3.1 ± 3.3 g/l; p < 0.006), D-Dimer (263.0 ± 379.9 µg/l; p < 0.001), vWF-AG (57.1 ± 81.6%; p < 0.001) and IPA (5.0 ± 9.8 ng/ml; p < 0.001) were observed in fainters during HUTT. APTT shrank ≥50% in 63% (CI 95%; 61-65%) of pts, and PAI-1 decreased in 75% of patients. Fibrinogen concentration rises during HUTT in 76% of pts, d-Dimer – in 86.6% of pts, vWBI – in 69.2% of pts ant IPA – in 71.8% of patients. In patients with negative HUTT only significant decrease of PAI-1 serum level was observed (6.8 ± 4.4 ng/ml; p < 0.04). Changes of values of measured parameters during HUTT did not correlate with age of pts. Observed changes in clotting related to the orthostatic stress resembles changes occurred during haemorrhage. Only activation of fibrinolysis simultaneously to
clothing provoked by orthostatic stress may prevent against dangerous thromboembolic complications in patients with vasovagal syncope.  

**Conclusions:** 1. Syncope induced by orthostatic stress during head-up tilt test lead to potentially dangerous activation of clotting in patients with vasovagal fairs.  
2. Simultaneous activation of fibroblasts processes by orthostatic stress prevents against dangerous thromboembolic complications in patients with vasovagal syncope.  
3. Endothelium-dependent activation clotting and fibrinolysis in response to orthostatic stress seems to play an important role in pathogenesis of vasovagal syncope.

**P4747**  
Incidence of permanent atrioventricular block in patients with syncope and bifascicular block  
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**Introduction:** In patients with syncope and bifascicular block (BBF), syncope is likely to be attributable to paroxysmal atrioventricular block (AVB). Therefore, a pacemaker implantation is recommended by current guidelines. However, it remains unclear if and at which time point a permanent blockade of atrioventricular (AV) conduction occurs and if pacemaker with AV management are useful in these patients.

**Methods:** 106 patients with either syncope with bifascicular block (group 1, n = 34) or paroxysmal AVB with (group 2, n = 51) or without BFB (group 3, n = 21) were included in the study. All patients received a pacemaker with AAI-SafeP, Symphony®, Sorin SPA, Milano, Italy) and were follow-up in a six-months-interval (mean follow-up 20±2 months). The primary end-point was the time to permanent switch to DDD-, DDI-, or VVI-mode.

**Results:** 44% of patients in group 1, compared to 70% in group 2 and 77% in group 3 had episodes of intermittent switches to ventricular pacing modes (p<0.056). The proportion of ventricular pacing was significantly higher in group 2 (40%) and group 3 (32%) compared to group 1 (17%) (p=0.02). The primary end-point occurred in 16% patients in group 1, 56% patients in group 2, and 53% patients in group 3 (p=0.001). Time to primary end-point was not significantly different between the groups (17.5±5 vs. 12.3±3 vs. 11.3±3 months; p=0.633). Documented paroxysmal AVB before pacemaker implantation was a significant predictor of the primary end-point (hazard ratio 4.86; 95% confidence interval 95% CI: 1.88-12.5; p=0.01). No other clinical or electrophysiological variables were predictive for the primary end-point.

**Conclusion:** Only 16% of patients with syncope and bifascicular block lose permanent AV conduction compared to 55% of patients with paroxysmal AVB.

**P4748**  
Prevalence of depression syndrome in patients with vaso-vagal syncope  
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The aim of study was analysis of factors influencing on the prevalence of depression syndrome (DS) in patients with vasovagal syncope (VVS).

**Study population:** We observed 650 pts (386 women, 264 men) aged 18-72 (median of age 41.5yrs), with VVS referred to head-up tilt test (HUTT).

**Methods:** All pts underwent HUTT performed acc. to standard Westminster or Italian protocols. Before HUTT the Depression Beck Score questionnaire was applied to all pts for evaluation of presence of DS. Mild DS was diagnosed if Beck Score ranged between 10 and 19, mild 20-25 and severe SD – with Beck Score ≥26 and higher.

During HUTT regional saturation (rSO2) of frontal lobes of brain was measured using INVOS cerebral oximeter in all pts. Changes of rSO2 during HUTT was expressed as a relative decrease (in%) of rSO2 in left and right channels in relation to the baseline value of rSO2. Univariate and multivariate analysis were performed for evaluation of the influence of age and gender, number of syncope and presyncope episodes, duration of disorder, CSSS results, type of vaso-vagal response during HUTT and duration of total, passive and active phases of HUTT on the occurrence of depression syndrome in patients with VVS.

**Results:** Depression syndrome was diagnosed in 275 pts (42.3%). Mild DS was observed in 30.9% of cases (201 pts), moderate DS – in 32 (4.9%) persons and severe DS was noticed in 67 (6.2%) pts. Significant influence of older age (F-5,8; p<0.002), higher number of syncope (F-4,1; p=0.04), longer time from first syncope (F-16,9; p=0.0001) and type of vaso-vagal response during HUTT (F=3,8; p=0.04) on prevalence of depression syndrome in patients with VVS was provoked. Pts with DS more frequently presented positive HUTT result and vasodepressive response to orthostatic stress than pts without DS. Patient with severe DS presented higher rate of cardioinhibitory response during HUTT.

There were no significant influence of gender, number of presyncope episodes, duration of HUTT (all phases), oxygen saturation of brain during HUTT and CSSS results on DS occurrence in patients with vaso-vagal syncope.

**Conclusions:** 1. Depression syndrome is relatively frequent in patients with vaso-vagal syncope.  
2. Occurrence of depression syndrome, in spite of age correlation, is also related to intensity of syncope and duration of the disorder and may be related to the type of vaso-vagal response to orthostatic stress during HUTT.

3. Cardioinhibitory response to the orthostatic stress during head-up tilt test occurred significantly more frequent in patients with diagnosed severe depression syndrome.

**Figure 1. Kaplan Meier plot**

**P4749**  
The CHADS2 risk score predicts long-term outcome after first admission for syncope - A nationwide study  
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**Background:** The CHADS2 score is an important risk stratification tool for risk of stroke in patients with atrial fibrillation and may also be predictive for other major cardiovascular events. We investigated if CHADS2 score could be applied as a risk stratification tool for predicting cardiac events after an episode of syncope.

**Methods and results:** All patients admitted with a first time diagnosis of syncope from 2001 to 2009 were identified from nationwide administrative registers in Denmark. Risk of major cardiovascular events (acute myocardial infarction or implantation of pacemaker/ICD) and all-cause or cardiovascular death according to CHADS2 score was analyzed by multivariable Cox proportional-hazard models. A total of 88,355 patients were included (median age 64 years (IQR:47.5-80.5) and 47.6% were males. There were a total of 19,011 deaths of which 10,389 (54.6%) were cardiovascular. The event rate of cardiovascular death was 5.25 per 1000 person-years for the group with CHADS2 score=0. The risk of cardiovascular death was significantly increased with increasing CHADS2 score when adjusted for sex (CHADS2 score=1-2 HR=10.25 [CI: 9.60-10.94], CHADS2 score=3-4 HR=23.59 [CI: 21.96-25.35], CHADS2 score=5-6 HR=36.82 [CI: 32.08-42.35], p<0.0001). This pattern was similar for all-cause mortality and major cardiovascular events.

**Conclusion:** The CHADS2 score significantly predicts risk of cardiovascular death, all-cause mortality and major cardiovascular events in patients admitted with syncope, and may be used for risk stratification in combination with other risk score systems. A CHADS2 score of 0 is associated with a very low long- and short-term mortality.
**Pictureconomics: a micro-costing analysis of unexplained syncope**

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**Purpose:** To quantify the resource use associated with unexplained syncope in a real-world setting, before a clinical decision to implant an implantable loop recorder (ILR) was made.

**Methods:** PICTUREconomics is based on PICTURE and a UK micro-costing study to quantify the burden of investigation and understand actual ‘bottom-up’ costs of each test. The previous history of healthcare contacts and investigations were captured. Types and volumes of 17 predefined diagnostic tests were recorded. Patients then received ILRs and were followed until a symptomatic event or a clinically scheduled visit (35-65 months after implant).

**Results:** The mean number of tests before ILR implant was 17 (95% CI 16.08 – 17.04) while the median was 13 (IQ Range 9 – 20). The minimum number of diagnostic tests observed was 0 while the maximum was 203. Among the top 25% of healthcare resource users, the median tests were 27 (IQ Range 22–36). Based on the tag-on micro-costing study, the mean expenditure per patient was £1,613.15 (€1,879.19) (± £568.97 – £2,246.22), while the costs escalated up to £7,417.89 (€8,624.66). The cost of a patient receiving every type of the 17 investigations once, including e.g. ECG, Holter, blood pressure provocation, TILT test, neurological evaluation, coronary angiography (MRA), CT, invasive EP testing etc., would have been £4,007.81 (€4,669.54). Should ESC Guidelines have strictly been adhered to (as was the case in 12% of the PICTURE Study population), the mean diagnostic test cost per patient per admission would be £710.3 (€827.58). In the remainder of patients, the same cost was £1,348.47 (€1,571.12).

**Conclusions:** More patients were more thoroughly investigated before ILR implant than in guidelines. PICTUREconomics showed the costs of investigations to be highly significant and most patients having moderate consumption while others consumed several times more. Identification of resource-intensive patients can be an algorithm for choosing a more cost-effective approach before an ILR implantation.

**Remote monitoring of implantable loop recorders: high artefact in the early phase following implant**

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**Purpose:** Implantable loop recorders (ILRs) are increasingly used in the investigation of unexplained syncope. Remote monitoring of ILRs has recently become available. We report our initial experience with the practical aspects of remote monitoring of ILRs.

**Methods:** Between August 2011, 10 patients were offered remote monitoring using the Medtronic Carelink system at the time of Reveal XT ILR implant. Scheduled transmissions were planned weekly for 8 weeks, then monthly. Patients were asked to make an appointment after a symptomatic episode. Time taken to download, review and report results to patients was recorded. Data from existing patients using Carelink after Reveal implant was also analysed; these patients made ad-hoc transmissions.

**Results:** 19 patients were enrolled, mean age 49.5 years. 18 successfully made a test transmission; there were technical difficulties in 1 patient resulting in 4 missed transmissions. 2 other patients missed a total of 3 transmissions. 134 scheduled transmissions were made; 2093 automatically detected episodes were recorded, all false positives. The majority of the episodes occurred in 2 patients. 1570 episodes of asystole were recorded in 1 patient due to artefact as a result of the autogain feature. In another patient, 401 episodes were detected as AF due to frequent atrial ectopics. Staff time requirements are shown in Table 1. Three patients made recordings after symptoms but no abnormality was identified. Nine patients already using Carelink sent ad-hoc/summation transmissions only. 44 transmissions were received; 23 VT episodes in 1 patient and 257 AF episodes in another patient; all were artefact. 9 symptomatic recordings were made; 1 patient received a pacemaker, all others were artefact.

**Conclusions:** Our data show a high incidence of artefact in the early phase after ILR implantation resulting in multiple recordings. Staff time to process, report and communicate data was 5.3 minutes per transmission.

**In patients with vasovagal syncope the increase of adrenomedullin during the positive head-up tilt test correlates with HRV parameters**

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**Background:** The mechanism regulating adrenomedullin (ADM) secretion - a strong vasodilating peptide - is little known. The activation of sympathetic nervous system causes rise of blood pressure due to increase of peripheral vascular resistance, what can be the impulse for ADM secretion. The strong activation of sympathetic nervous system is considered as a cause of syncope in vasovagal patients. The aim of the study was to assess the relation between the changes of ADM plasma level during HUTT and heart rate variability parameters in patients with vasovagal syncope due to cardiovascular reaction after nitroglycerine provocation.

**Material and methods:** The studied group consisted of 17 patients (pts) with vasovagal syncope (vvs) due to cardiovascular reaction during active phase of HUTT (after NTG provocation). In all studied pts blood samples for ADM level assessment were drawn before the test, after 30 minutes supine rest, and immediately after the syncope. Adrenomedullin plasma level was assessed using radioimmunological assay. The patients had 24-hour ECG Holter monitoring and time domain HRV analysis was performed for 24 hours, night and day time.

**Results:** In the study group there was no correlation of HRV parameters and mRR with age of pts. The mRR was significantly shorter in women than in men (p<0.05). After selected sex in the study group there was no correlation of ADM parameters and mRR with age of pts. There was significant negative correlation between ADM level changes during HUTT (ADMA/ADM1) and mRR during the all 24 hours (r=-0.55 p<0.05), night (r=-0.52 p<0.05) and day time (r=-0.54 p<0.05), negative correlation with pH, p<0.5 p<0.05, SDNN (r=-0.51 p<0.05) and pNN50 (r=-0.54 p<0.05).

**Conclusions:** In the studied population mRR and ADM parameters do not correlate with age of pts. 2. In pts with vasovagal syncope the ADM/ADMA/ADM1 correlates with HRV parameters in the time period in which the patients remain free from any signs of neurocardiogenic reactions and gravitational stress.

**The influence of the menstrual cycle on the tilt testing result**

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**The fluctuation of the female sex hormones level may change the susceptibility to the neurocardiogenic reflex provocation throughout the menstrual cycle.**

The aim of the study was to assess the distribution of the positive tilt testing (TT) results through menstrual cycle as well syncope and presyncope and finally to determine if the phase of menstrual cycle contribute to the duration of the loss of consciousness during TT induced syncope.

**Material and methods:** The study group consisted of 183 premenopausal, women aged 29.5±7.8 years. The menstrual cycle was divided into 4 phases based on the first day of the last menstruation (Menstrual (M), periovulatory (F), periovulatory (O) and postovulatory (L)). The clinical characteristics and TT results are shown in the table:

<table>
<thead>
<tr>
<th>Group</th>
<th>Menstrual phase (M)</th>
<th>Periovulatory phase (F)</th>
<th>Periovulatory phase (O)</th>
<th>Postovulatory phase (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=49</td>
<td>n=54</td>
<td>n=39</td>
<td>n=41</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.4±7.4</td>
<td>31.0±7.5</td>
<td>31.3±7.5</td>
<td>31.6±8.4</td>
</tr>
<tr>
<td>Positive TT (%)</td>
<td>72±8.5</td>
<td>71±8.4</td>
<td>71±8.5</td>
<td>71±8.9</td>
</tr>
<tr>
<td>Syncope duration (s)</td>
<td>41±16.4</td>
<td>30±10.5</td>
<td>30±10.5</td>
<td>30±10.5</td>
</tr>
</tbody>
</table>

**Conclusions:** The distribution of the positive and negative TT results as well syncope and presyncope as a TT result does not differ throughout the menstrual cycle. 2. The duration of the loss of consciousness is longer during perimenstrual phase of the menstrual cycle independently from the higher syncope number and lower heart rate at TT termination. 3. The fluctuation of the female sex hormones levels does not change the susceptibility to the neurocardiogenic reflex provocation but when provoked influence on its course.
PERCUTANEOUS CORONARY INTERVENTION: INVASIVE IMAGING/DEVICES AND TECHNIQUE

P4754

Head to head comparison of fully drug-free bioresorbable PLA and bare metal stents in normal porcine coronary: a six-month angiography and OCT follow-up study
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Background: The concept of fully bioresorbable polyactic (PLA) stent is now perceived as a potential attractive alternative to metallic stent. The aim of this study is therefore to evaluate a drug-free PLA stent in the porcine model as compared to a bare metal stent (BMS).

Methods: Twenty-nine BMS (Vision®, Abbott, Inc; 3X12 mm) and 29 PLA stents (ART, Noisy le Roi, France, 3X11mm) were implanted in porcine coronary arteries. QCA and OCT analysis were performed immediately after stent implantation, and repeated 1 (n=22), 3 (n=28), and 6 (n=8) months later. The primary end-point was in-stent diameter by OCT, and the secondary end-points were acute recoil and late lumen loss (LLL).

Results: Acute recoil was not significantly different between PLA and BMS groups (3.6±6.1% vs. 4.7±5.3%, respectively, p=NS). In-stent diameter was closely similar immediately after stent implantation in PLA and BMS groups (2.99±0.08 mm vs. 3.05±0.18 mm, respectively). BMS in-stent diameter remained constant through 6-month follow-up (2.99±0.21, 2.95±0.21, 3.14±0.21 mm at 1, 3, and 6 months, respectively). In contrast, in-stent diameter significantly increased at 3 and 6 months in the PLA group indicating late positive remodeling at 3-6 months, and in-stent diameter was 0.14 mm vs. 0.16 mm, respectively. BMS in-stent diameter was 0.24 mm vs. 0.21 mm, p=NS).

Conclusion: The volume of lipid-rich plaque associated with amount of released plaque particle during procedure-related released debris captured by filter device. These findings provide insight into the mechanisms of distal embolism during PCI.

P4757

Nine months optical coherence tomography evaluation of neointimal coverage of a strategy of paclitaxel-eluting balloon plus bare metal stent
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Background: Drug-eluting balloon (DEB) predilatation followed by bare metal stent (BMS) implantation represents an innovative treatment for coronary artery disease. Yet, the safety of this strategy has still to be demonstrated.

Methods: Frequency-domain optical coherence tomography was performed at 9 months in a registry of 30 consecutive patients who underwent elective stenting with a BMS (Prokinekt, Biotronik) after predilatation with a DEB (Elutax, Aachen Resonance). Patients with clinical restenosis (n=3), or with suboptimal images (n=4) were excluded. Quantitative strut level analysis was performed at 0.4-mm intervals (every other frame) along the entire target segment. A total of 23 lesions in 23 patients were analyzed. The center of the luminal surface of the strut blooming was determined for each strut, and its distance to the lumen contour was calculated automatically to determine strut-level intimaling thickness (SIT). Struts covered by tissue had positive SIT values whereas uncovered or malapposed struts had negative SIT. The number of struts without coverage was counted for each frame analyzed, and the total number of frames with uncovered struts was recorded. Strut malapposition was determined when the negative value of SIT was higher than 100 micron (60 μm). Prokinetic strut thickness, plus a correction factor of 40 μm to account for strut blooming.

Results: A total of 4304 struts were analysed. In total, 131 struts (3%) in only 2 lesions (123 in one, 8 in the other) were found to be uncovered. Malapposed struts were 105 (2.4%) of 4048 (7%). Percentage net volume obstruction was 30±15.6%.

Conclusions: BMS implantation plus DEB is a safe strategy, as it is associated with a percentage of malapposed/ uncovered struts which compared favourably with BMS historical controls. Neointimal regrowth (after the exclusion of clinical restenosis patients) is also comparable to historical data.

P4755

The volume of lipid-rich plaque, measured by integrated backscatter IVUS was associated with amount of captured plaques by filter-type distal protection device during coronary intervention
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Background: The atherosclerotic plaque disruption caused by balloon or stent expansion and distal embolism may major cause of peri-procedural myocardial injury during percutaneous coronary intervention (PCI). However relationship between details of lesion characteristics and amount of released plaque particle during procedure is unclear.

Methods: From April 2010 to December 2011, thirty consecutive patients who underwent PCI with filer-type distalprotection device (FilterWire™) following integrated backscatter intravascular ultrasound (IB-IVUS) analysis were enrolled. The volume of each plaque component (lipid, fibrous and calcified) within target lesion was calculated. Area of captured debris of protection filter was measured by microscopic evaluation (Figure). The coronary flow disturbance (TIMI 0/1/2) during distal protectionwas defined as filter-related flow disturbance (FFD).

Results: The lipid volume of target lesion significantly correlared with area of captured debris (r= 0.41, p= 0.02). The fibrous volume and calcified volume did not correlate with area of captured debris. The lipid volume of patient with FFD was significantly higher those without FFD (160±390.2 mm³ vs. 93±55.6mm³, p<0.01). The lipid volume was independently correlated with area of captured debris in multivariate regression analysis after adjustment for clinical, procedural parameters and other plaque components.

P4758

Intravascular ultrasound guided everolimus eluting stent implantation resolves the disadvantage of thin strut cobalt chromium platform in patients with diabetes
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Background: Though efficacy of everolimus-eluting stent (EES; Xience V) is well-established by many clinical evidences, several trials failed to show superiority in diabetic subset. We hypothesized that inappropriate stent expansion in complex lesion of diabetes due to thin cobalt chromium platform may be one of the reasons. The purpose of this study is to investigate this hypothesis using intravascular ultrasound (IVUS).

Method: Consecutive 130 de-novo lesions (61 EES and 69 paclitaxel-eluting stent (PES; Taxus Express2, stainless steel thick platform)) treated by elective IVUS-guided PCI for stable patients were recruited in this study. Stent size was determined according to pre-procedural IVUS findings. After stent deployment using standard technique, IVUS procedure was repeated and stent diameter and cross-sectional area (CSA) were measured. If stent expansion was inadequate,
post dilation was performed using short-length high pressure balloon and again IVUS was performed. IVUS findings were then compared with estimated diameter and CSA calculated from each stent compliance chart.

Result: In EES, there were significant differences of stent expansion and symmetry index between diabetic and non-diabetic just after stenting. However, these findings were not observed in PES. According to IVUS findings, 79% of diabetic cases in EES group required post balloon dilation to obtain optimal stent expansion. After post dilation, difference between diabetic and non-diabetic did not appear in EES.

Conclusion: In EES, asymmetrical stent underexpansion was observed in diabetic patient after stent deployment, however, IVUS-guided post-dilation resolved this disadvantage. IVUS-guided EES implantation can improve clinical outcome in patients with diabetes.

Feasibility and efficacy of ex-vivo stent fracture detection by optical coherence tomography (OCT) and microcomputed tomography (microCT)

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Purpose: Coronary stent fracture (SF) is recognized as a contributor to adverse clinical events like stent restenosis. However, the true prevalence of coronary SF remains uncertain with clinically observed fracture rates of up to 8% in vivo utilizing fluoroscopic detection and up to 70% at autopsy using high resolution x-ray and three-dimensional (3D) microCT. There is limited data to suggest that intravascular ultrasound may improve the sensitivity of in-vivo stent fracture detection, however, to our knowledge there are no controlled studies to demonstrate the sensitivity of cross-sectional intravascular imaging for SF detection.

Methods: A bench top fracture model was created by manually cutting stent crowns or interconnectors (Abbott Multilink Vision 3.0 x 12 mm and Biotronik, PRO-Kinetik, 3.0 x 10). A total of 7 stents with varying extent of fracture were implanted in silicone tubes and analyzed with optical coherence tomography (OCT) (100 fps, 10 mm/sec, Dragonfly, St. Jude) and microCT (eXplore, GE). Two experienced, blinded interventional cardiologists reviewed the 2D-OCT pullback scans, 2D- and 3D-micro CT reconstructions looking for SF. The review procedure was limited to 5 minutes per stent/modality to simulate a realistic clinical decision time. The sensitivity and specificity of each modality was determined based on the known fracture sites as visualized through the clear silicone tubes.

Results: Review of the 2D OCT images accurately identified 4/9 SF (sensitivity 44.4%) with no false positive SF detection (specificity 100%). Review of the 2D microCT images accurately identified 6/9 SF (sensitivity 68.9%) with no false positive SF detection (specificity 100%). Review of the 3D microCT renders accurately identified all of the SF (sensitivity 100%) with no false positive SF detection (specificity 100%). Interobserver variability was moderate for OCT and perfect for 3D microCT (κ = 0.55 and 1.0 respectively).

Conclusion: Based on this small bench top series, clinically available 2D cross-sectional imaging with OCT is inadequate to reliably detect coronary SF. The vast superiority of microCT to detect SF explains the gap between the clinically reported prevalence of SF as compared to autopsy studies. We chose OCT over IVUS given the improved temporal and spatial resolution, however, even with OCT wire artifacts may have limited SF detection. Given the 100% sensitivity of 3D microCT for SF detection there remains the potential for high-resolution axial imaging like OCT to be rendered in 3D to improve SF discrimination and ultimately may garner a more comprehensive understanding of the natural history and impact of SF.

Neointimal appearance of late clinical event related lesions after bare-metal stent and sirolimus-eluting stent implantation assessed by Optical Coherence Tomography

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Background: Late clinical event such as very late stent thrombosis (VLST) and late in-stent restenosis (ISR) after bare-metal stent (BMS) and drug-eluting stent (DES) is an important clinical issue. However, the difference of underlying mechanisms in late clinical event between BMS and DES has not been fully evaluated yet. The aim of the present study was to compare neointimal tissue appearance of these lesions between BMS and sirolimus-eluting stent (SES) by using optical coherence tomography (OCT).

Methods: We examined the neointimal tissue appearance in 34 late clinical event lesions after BMS (n=15) and SES (n=19) implantation by OCT. Late clinical event was defined as VLST and late ISR (>1 year after initial procedure).

Results: Results were shown in the table described below.

<table>
<thead>
<tr>
<th></th>
<th>BMS (n=15)</th>
<th>SES (n=19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neointimal disruption, n (%)</td>
<td>3 (20)</td>
<td>5 (26)</td>
<td>0.032</td>
</tr>
<tr>
<td>Stent malapposition, n (%)</td>
<td>0 (0)</td>
<td>5 (26)</td>
<td>0.032</td>
</tr>
<tr>
<td>Calcification within neointima, n (%)</td>
<td>3 (20)</td>
<td>0 (0)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Values are given as n (%) or mean ± SD. BMS = bare-metal stent; OCT = optical coherence tomography; SES = sirolimus-eluting stent; TGFA = thin-cap fibroatheroma.

Conclusions: In late clinical event related lesions, atherosclerotic change such as TGFA formation and calcification within neointima is often demonstrated in BMS and stent malaposition might be related in DES.
**Sex-related differences in percutaneous coronary interventions for chronic total occlusions**

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**Purpose:** The aim of this study was to assess sex-differences in percutaneous coronary intervention (PCI) for chronic total occlusions (CTO).

**Methods:** The study included all consecutive patients undergoing PCI for CTO at 3 tertiary PCI centres between January 2004 and December 2011. A multi-variable mixed effect logistic regression for clustered data was used to assess the variables, CTO lesion difficulty, vessel site, and procedural techniques. CTO lesions were graded as easy (score of 0), intermediate (score of 1), difficult (score of 2), and ‘very difficult’ (score of ≥3), according to the J-CTO score on the basis of calcification, bending, blunt stump, occlusion length ≥20 mm, and previously failed lesion.

**Results:** Among 1261 patients, median age 63 yrs-old (25th-75th percentile, 55-72), undergoing PCI for 1418 CTO, 176 (13.9%) were women. Women, as compared to men, were significantly older (70.5 yrs-old (61-77) vs 62 (55-72), p<0.001), less frequently smoker (15.3% vs 28.8%, p<0.001), and had less frequency a previous coronary artery bypass graft surgery (2.8% vs 8.1%, p=0.01).

In a lesion-based analysis, left anterior descending artery as the treated vessel, was more common (36.5% vs 26.4%) and left circumflex artery was less frequent (15.6% vs 23.8%) among women (p=0.03). The prevalence of J-CTO score ≥3 was lower among women than in men (34.9% vs 43.8%, p=0.02). No differences between the two groups in the prevalence of bridging or side branch at the occlusion site, and Rontop collateral circulation were present, although the use of retrograde approach tended to be lower in women (6.8% vs 10.6%, p=0.1).

Success rate was higher in women (77.1% vs 70.1%, p=0.049). However, multivariable logistic regression female sex was not found to be a significant predictor of PCI success (odds ratio 1.31, 95% confidence interval 0.89-1.94, p=0.17).

**Conclusions:** In this registry of patients undergoing PCI for CTO, women presented a higher PCI success rate as compared to men that could be largely explained by a lower lesion complexity. Indeed, female sex did not emerge as an independent predictor of PCI success.
Germany) followed by bare-metal CoCr stent implantation (Prokinetic, Biotronik, Berlin, Germany) (PEB-CoCr-stent group) versus implantation of everolimus-eluting stent (Xience, Abbott Vascular, Redwood City, CA) (DES group) in the treatment of de-novo stenosis in native coronary artery.

**Methods:** The study, randomized, single center, was planned to enroll 366 patients, 188 patients per arm, with stable angina, undergoing percutaneous coronary intervention of a de-novo stenosis less than 15mm in length in a native coronary artery. Primary endpoint, in a non inferiority study design, was 9-month binary angiographic restenosis. Combined antiplatelet treatment was to be continued for 3 months in PEB-CoCr stent group and 12 months in DES group.

**Results:** The study was stopped after enrollment of 125 patients, 59 in the DES group and 66 in the DES group, due to excess of Target Lesion Revascularization (TLR) in the PEB group (14% in the PEB vs 2% in DES group; p=0.001). No significant differences in terms of clinical or angiographic characteristics were observed among the two study groups. No stent thrombosis occurred in both study groups.

**Conclusion:** In the treatment of de-novo coronary stenosis, a strategy of predilatation with Elutax PEB prior to bare-metal CoCr stent implantation was significantly inferior to implantation of Xience stent in terms of 9-month target lesion revascularization.

**P4770** Thin-strut stent is favorable for severe calcified lesion needing rotational atherectomy in real world

**Percutaneous Coronary Intervention**


**Background:** Percutaneous coronary intervention (PCI) on severe calcified lesion is still challenging. There are a few studies about outcomes after PCI with drug-eluting stents (DES) on severe calcified lesion. The aim of this study is to clinically evaluate a feasible thin- or thick-strut stents to calcified lesion after rotational atherectomy including hemodialysis patients and long lesion.

**Methods:** Sixty-six consecutive patients (115 stents) with DESs for severe calcified lesions which needed rotational atherectomy before stent implantation were enrolled. We divided them into the following two groups according to strut thickness: thick-strut group (strut-thickness; ≥100μm) and thin-strut group (<100μm). Follow-up angiography was performed at 6 to 10 months after PCI. We compared late lumen loss by quantitative coronary angiography and target vessel revascularization (TVR) rate, in addition to incidence of hemodialysis, diabetes mellitus, hypertension and dyslipidemia, and stent size, lesion length and number of stents, between the two groups.

**Conclusion:**TVR rate was significantly lower in thin-strut group than in thick-strut group while there were no differences of the other parameters between two groups.

**P4771** Differential determinants of early stent thrombosis in drug-eluting and bare metal stents: ex vivo human autopsy study

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**Background:** Early stent thrombosis (ST) in patients with acute coronary syndrome (ACS) remains an ongoing problem for both drug-eluting stents (DES) and bare-metal stents (BMS). Potential mechanisms associated with stent placement relative to underlying lesion histomorphology are not well understood.

**Methods and Results:** Stented lesions (n=62) from 59 patients presenting with ACS and dying within 30 days were eligible for the histological assessment. Histologic cross-sections prepared at 3 mm intervals were evaluated for stent thrombosis (ST), strut malapposition, media disruption, and necrotic core prolapse in addition to other potential indicators of early ST such as the underlying plaque morphology and vessel/lesion area.

Early thrombosis was identified in 17 of 45 drug-eluting and 20 of 37 bare stents. There were no significant differences in the stented artery or relative location within the vessel with usage of DES versus BMS. In a "per section" analysis, 56 of 293 sections from DES showed evidence of luminal thrombosis compared with 62 of 287section from BMS. Stut malapposition was similarly seen for DES with or without early ST, respectively (29% vs 26%, p=0.60) while the incidence for BMS was significantly greater in those with early ST (37% vs 19%, p=0.004).

On the contrary, media disruption was more likely associated with thrombosis for DES (39% vs 18%, p=0.002) while difference among BMS was of borderline significance (19% vs 11%, p=0.08). Necrotic core prolapse was significantly higher for BMS exhibiting thrombosis (26% vs 13%, p=0.018) while no significant difference was noted for DES (16% vs 10%, p=0.25).

In morphological analysis, the percentage of struts with underlying medial disruption (40%) and thin-strut (28%) vs. 21% (thrombosis) vs. 16% (no thrombosis), p=0.002) were more likely correlated with early ST.

**Conclusions:** Autopsy data indicate divergent mechanisms of early ST between drug-eluting and bare metal stents. Although these differences may be partly explained by differences in strut thickness, it is clear that other factors are involved as well, and further studies should be undertaken to elucidate the mechanisms involved.

**Angiographic outcomes of everolimus-eluting stent as compared to sirolimus-eluting stent: a sub-study of the RESET trial**

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**Objective:** This study is aimed to clarify the difference in the angiographic findings of Everolimus-eluting stent (EES) as compared to the first generation Sirolimus-eluting stent (SES).

**Methods:** RESET is a prospective multicenter randomized open label trial comparing EES with SES in Japan. The trial was designed as ‘all-comers’ trial. Out of 3197 patients of total cohort, 571 patients were enrolled in the angiographic sub-study. Angiograms were assessed qualitatively and quantitatively both at procedure and at 8-12month in the independent corelab.

**Results:** Baseline demographics were not different except for stent length, and follow-up results were not different between the 2 groups except for the late loss of proximal edge (table). Edge restenosis was mainly observed in EES group, whereas edge thrombosis was dominant in SES group. Stent fracture was only observed in 1.2% of the SES cases (p=0.042), and peri-stent contrast staining (PSS) as a presentation of incomplete stent apposition during PCI was observed in 1.5% of EES cases and 3.6% of SES group (p=0.177).

**Conclusions:** Angiographic outcomes of EES and SES were similar. However, restenotic pattern and detrimental findings such as stent fracture and PSS were different between the 2 groups.

**P4772** Stent maximal expansion capacity with current DES Results: a platform critical for left main stent selection?

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**Background:** Coronary stents are usually manufactured in only 2 or 3 different “Workhorse” platforms: a critical factor for left main stent implantation.
Is there an advantage in using second vs. first generation drug eluting stents in acute coronary syndromes?

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Purpose: Registry series and RCTs show that DES have an overall better performance than BMS in patients treated in the clinical context of an acute coronary syndrome (ACS), both STEMI and NSTEMI/UA, mainly by reducing TLR. Whether or not the use of 1st generation DES (DES1g) versus 2nd generation DES (DES2g) differs in this particular setting is largely unknown.

Methods and analysis: In a single center prospective registry, 5266 patients were submitted to PCI with at least 1 DES from January 2003 to December 2009. Of these, 1423 (43.6%) were treated in the setting of an ACS with either DES1g only (paclitaxel or sirolimus; n=953 [64.9%]) or DES2g only (n=500 [35.1%]). The primary outcome measure was the occurrence of death, myocardial infarction (MI) or target vessel failure (TVF), whichever came first; repeat revascularization of the index stented lesion (TLR) and the occurrence of definite stent thrombosis (according to the ARC definition) were assessed as secondary outcomes.

At a median follow-up of 598 days (IQR range 453; 1206), the incidence of death was 8.8% (286), 220 pts (6.7%) had MI and TVF events occurred in 349 (10.7%). Disparity of follow-up duration was accounted for by considering only one year composite MACE (n=290; 8.9%). After adjusting for baseline characteristics (age, hypertension, tobacco use, previous CABG and the Syntax score), using a Cox proportional hazard model, we could not find a significant difference in the MACE rate between DES1g (8.9%) and DES2g (8.7%) patients (HR 1.1; 95% CI 0.82-1.56; p=0.46). Repeat target lesion revascularization was non-significantly inferior in DES2g (3.1% vs 3.3%; HR 0.96; 95% CI 0.63-1.47; p=0.85) in a per-patient analysis, at one year, ARC-definite stent thrombosis was documented in 1% of DES2g vs 2.8% of DES1g pts (corrected HR 0.37; 95% CI 0.14-0.97; p=0.0042)

Conclusions: Our results suggest that in patients submitted to PCI with DES implantation in the setting of acute coronary syndromes, both 1st and 2nd generation devices seem to be similarly effective, despite a statistically higher incidence of ARC-definite stent thrombosis with 1st generation DES.

Stent selection at a particular diameter based on workhorse design may contribute to improving stenting results, particularly in left-main lesions treatment.

The anti-proliferative effect of atorvastatin is dependent on stent surface material

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The proliferation and migration of arterial smooth muscle cells (SMCs) are key events in the formation of neointima that frequently follows percutaneous coronary intervention (PCI). Beside the clinical benefit, Statins have an anti-proliferative effect on SMCs and stabilize arteriosclerotic plaques. To optimize controlled drug delivery and release, new biodegradable polymer stent coatings are currently being developed. The impact of Statins on cell proliferation of endothelial cells (ECs) and SMCs on biodegradable polymers has not been studied yet.

Thus, we assessed EC and SMC proliferation, viability, and uptake of 14C-atorvastatin by BnU-ELISA, AlamarBlue®-Assay, and Radio-Assay, respectively. Primary endothelial cells (HCAEC) and smooth muscle cells (HCASMC) were incubated with concentrations of Atorvastatin ranging from 0.01 μM up to 10 μM for 48 hr. Additionally, HCAEC and HCASMC were cultured on different polymer surfaces. Comparable evaluation was performed with polymers similar to those utilized in DES that are currently being marked (PEVA, PBMA, and PLLA).

Atorvastatin showed a dose-dependent inhibition of EC and SMC proliferation. At a concentration of 0.1 μM the proliferation of HCAEC remains unaffected whereas the proliferation of smooth muscle cells is significantly reduced. However, increasing Statin concentrations also affect endothelial cells which is of particular interest in the context of atherosclerotic plaques and incubated with Atorvastatin show a material-dependent effect of the Statin rather than a dose-dependent. On PEVA and PBMA (Cypher stent) proliferation of HCAEC is significantly decreased by nearly 90% (p=0.02), on PLLA HCASMC proliferation is reduced by 50% (p=0.05). Furthermore, PLLA-Copolymers seem to promote HCAEC proliferation and somehow inhibit the impact of Atorvastatin on SMC proliferation.

We demonstrate for the first time a material-dependent effect of Atorvastatin on the proliferation of HCAEC and HCASMC. It seems that recently designed polymers for new stent technologies do not support the anti-proliferative effect of Atorvastatin on SMCs. The development process of new stent surfaces, particularly bioabsorbable polymers should consider the analysis of interactions of frequently used drugs with the material.

One year outcome after PCI for distal left main stenosis treated with single stenting or with T-stenting


Background: Percutaneous treatment (PCI) of distal left main bifurcation may involve stenting of the main branch including final kissing balloon of the side branch or single stenting of the side branch. There is only limited data comparing single stenting including final kissing-dilatation versus T-stenting regarding the long term clinical follow-up.

Hypothesis: We tested the hypothesis that the lesions that were treated with the single stent have a lower target lesion revascularisation (TLR) 1 year after PCI than lesions treated with T-stenting.

Methods: We established a bifurcation registry of 394 consecutive patients undergoing percutaneous catheter intervention (PCI) for distal left main stenosis in our institution between January 2002 and december 2009. One stent approach was performed in 229 patients and T-stenting in 165 patients. The need for double stenting to achieve best angiographic result was 46%. Complete 1 year clinical follow-up of all patients is available for the analysis.

Results: Baseline clinical characteristics were well matched between 2 groups. Target lesion revascularisation (TLR) 1 year after PCI was performed in 11.7% of patients treated with single stenting and final kissing and in 13.5% treated with T-stenting (p=0.16). The combined endpoint of death and myocardial infarction (MI) as marker for safety was reached by 10.5% of patients in the single stent group and in 11.5% in the T-stenting group (p=0.56). Death occurred in 8.7% in the single stent group and in 7.8% in the T-stenting group (p=0.57).

Conclusions: PCI of de-novo distal left main stenosis using simple approach (single stenting with final “kissing balloon”-dilatation) is associated with similar 1 year outcome as compared with T-stenting.
Drug eluting stents with microporous polymeric covering as a scaffold for acquisition of extremely thin neointimal lying without disturbing branching vascular flow

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Objective: As new generation of drug eluting stents, we developed microporous polymeric-covered stents, whose design concept was utilization of covering for a scaffold for extremely thin neointimal lying. The effectiveness was demonstrated in this study for long-term animal experiments.

Methods and Results: Two types of covered stents based on different stent platforms of self-expandable stents (Luminex from Bard Co.; 5 mm x 20 mm) and balloon-expandable stents (Momo from Japan Stent Technology Co.; 3 mm x 20 mm) were prepared in three steps, that is 1) dip-coating of polyurethane for covering, 2) laser-induced microporing, and 3) drug coating with argatroban. The stents had structural advantage with flat luminal surface impregnating strut completely into the cover film. The stents were placed at carotid or subclavian arteries of beagle dogs or rabbits. Even at 1 month of implantation (n=5) the lumino-vascular flow perfectly due to microporing of cover film. Argatroban had strong anti-thrombogenic and anti-inflammation potentials.

Conclusion: Argatroban-loaded microporous covered stents developed here were effective for in long-term lying of extremely thin neointima with long-term highly reliability.

Comparison of 3-year clinical outcomes between classic crush and modified mini-crush technique in coronary bifurcation lesions

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Purpose: We aimed to compare long-term outcomes of modified mini-crush (modi-MC) technique with classic crush (Crush) technique for treating coronary bifurcation lesions. Modi-MC technique showed excellent procedural success immediately and good 9-months clinical outcomes. We aimed to compare 3-year clinical outcomes between 2 techniques.

Methods: From Jan 2000 to Nov 2009, we enrolled de novo bifurcation lesions treated with Modi-MC (n=112 lesions in 111 patients) and crush technique (n=69 lesions in 67 patients). Primary end-point was major adverse cardiac events (MACE), composite of all-cause death, myocardial infarction (MI), target lesion revascularization (TLR) and stent thrombosis at 3 years.

Results: There were no significant differences in baseline characteristics. After 3 years, MACE was significantly lower in modi-MC group (25.4 vs 13.5%, p=0.046). The incidence of all-cause death was 7.5% vs. 2.7% (p=0.16), MI was 4.5% vs. 0.9% (p=0.15), TLR was 17.4% vs. 8.9% (p=0.09) and stent thrombosis was 3% vs. 1.8% (p=0.63) in Crush and modi-MC group, respectively. However, MACE of left main (LM) lesion was significantly higher than non-LM bifurcation (35.7% vs. 12.9%, p=0.001) in entire cohort. Cox regression analysis showed LM location (p=0.002, odds ratio[OR] 3.031, 95% confidence interval[Ci] 1.526-6.021), and crush technique (p=0.044, OR 2.035, 95% Ci:1.018-4.069) were independent predictors for MACE.

Conclusions: Modified mini-crush technique was more favorable 3-year clinical outcomes comparing with classic crush technique. However, both classic crush and modified mini-crush techniques are cautiously applied in LM bifurcation lesion.

The ulcer puncture technique: lessons from experience

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Background: The Ulcer Artery (UA) could be a valuable approach for cardiac catheterization, but the “how to do” of the puncture have not been established. We propose “how and where” to puncture to the UA to reduce the incidence of complications.

Methods: We evaluated all patients (pts) in which the UA approach was at least considered from Jan-2002 till Oct-2011. All studies were performed by operators with experience in transradial approach. Follow-up was achieved in 95% pts at 24 hours and 91% at 3 months after procedure. Haematomas (H) and neurological complications related to the UA puncture were recorded.

Results: Of a total of 22425 pts attended, (73% radial approach) 1127 (5%) were performed via UA (mean aged 67±14 years. 65% males). Risk factors were the usual in the non-selected populations. UA was punctured at or near the wrist’s skin folds, or more proximal at 3-4 cm (the 2 sites where the artery can be felt best). Study was completed in 1025 pts (91% of attempted). In 113 pts (11%) UA was used after failure of radial puncture in the same wrist. The main cause of crossover to other artery was puncture failure (65% of cases). Out to 1513 procedures performed (77% by right UA), 661 (45%) were PCI. A total of 65 H > 10 cm were documented; 12 (12%) of them, within the first 100 cases done, and Concerned in the following 925 pts (5.3%) (p < 0.05). There were 3 temporary neurological complication related to the nerve compression by big H and 15% of unintentional nerve punctures without sequel at follow up (ulnar nerve runs just below the artery). In a Multi-Variable analysis, H was related to a proximal puncture site, that difficult the compression of UA.

Conclusion: Ulnar puncture must be done above the carpal bones (at the level of the wrist’s skin fold). Needle should be directed from lateral to medial in order to avoid unintentional ulnar nerve puncture. The high incidence of UA puncture failure is due to the difficulty to felt the artery by many pts, but when UA pulse is stronger than radial, could be even better option than radial for cardiac catheterization.
PERCUTANEOUS CORONARY INTERVENTION OUTCOMES

P4780 The impact of circadian variations on long-term clinical outcomes in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention
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Purpose: The circadian rhythm influences a number of cardiovascular physiological processes including the incidence of acute myocardial infarction. A circadian variation in infantile size has recently been shown in rodents, but there is no clinical evidence of its influence on long-term outcomes. The aim of this study is to investigate whether circadian rhythm could cause differences in long-term clinical outcomes in patients with STEMI.
Methods: A total of 3,561 STEMI patients with less than 12 hours of symptom onset were obtained from the Korea Acute Myocardial Infarction Registry and divided into 4 time groups based on time of symptom onset (period I: 00:00-05:59, period II: 06:00-11:59, period III: 12:00-17:59, and period IV: 18:00-23:59). The primary outcome was the composite of major adverse clinical events (MACE), defined as death, non-fatal myocardial infarction, and revascularization, at one-year.
Results: There was no difference between groups regarding baseline patient characteristics, angiographic findings, and procedural results. There was significant difference between groups regarding symptom-to-door time and door-to-balloon time with highest levels in patients with symptom onset of period I (251.7±182.1 min, p<0.001; 107.4±62.6 min, p<0.001, respectively). However, there was no significant difference between groups regarding maximum CK-MB and left ventricular ejection fraction. Total death and MACE were not different between groups during hospitalization (period I: 4.9%, period II: 5.1%, period III: 3.7%, period IV: 5.1%, p=0.410; period I: 5.9%, period II: 5.4%, period III: 4.4%, period IV: 5.2%, p=0.562, respectively) and at one-year (period I: 8.0%, period II: 8.6%, period III: 5.8%, period IV: 7.7%, p=0.103; period I: 14.6%, period II: 14.6%, period III: 12.0%, period IV: 14.0%, p=0.321, respectively).
Conclusions: This study showed that a circadian difference in symptom onset of STEMI did not influence in-hospital and long-term clinical outcomes. More data are needed to clarify the role of circadian variations on the long-term outcomes in patients with STEMI.

P4781 Impact of microalbuminuria on cardiovascular outcomes in patients with mild renal dysfunction who underwent elective PCI
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Background: Microalbuminuria (MIA) is considered an independent predictor of cardiovascular event. However, the impact of MIA on cardiovascular outcomes in patients with mild renal dysfunction is unclear. The aim of this study was to investigate the association between elevated urinary albumin excretion rate and clinical cardiovascular outcomes in patients with mild renal dysfunction who underwent elective PCI.
Methods: In this study, 120 consecutive patients with early stage CKD (eGFR 60-90 ml/minute/1.73 m²) who underwent elective PCI between November 2008 and April 2009 were enrolled. Urinary albumin to creatinin ratio (ACR; mg/gCr) was measured and population was divided into patients with MIA (ACR ≥30 mg/gCr, 39 patients) and those without MIA (ACR <30 mg/gCr, 81 patients). The endpoint of this study was defined as the composite of death, myocardial infarction (MI) and any revascularization.
Results: During a median follow-up of 10 years (2008-2017), 104 (86.7%) events occurred. Event-free survival was significantly higher in patients without MIA as compared to patients with MIA (74.1% vs 51.3%, p=0.012, log-rank test, Figure). There was no significant difference in the incidences of death or MI, target lesion revascularization between two groups. The incidence of revascularizations for new lesions was significantly higher in patients with MIA than those without MIA (13.6% vs 38.5%, p=0.019). Independent predictor of cardiac events identified by Cox proportional hazard model was MIA (hazard ratio 2.54; 95% CI. 1.203-5.352; p=0.014) after adjusted for age, gender, and conventional risk factors.
Conclusions: The elevated urinary albumin excretion rate is an independent predictor of adverse cardiovascular outcomes in patients with mild renal dysfunction who underwent coronary intervention.

P4782 High preprocedural total adiponectin levels are associated with poor long-term cardiovascular outcome after percutaneous coronary intervention
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Objective: Adiponectin is considered to possess antiatherogenic and cardioprotective properties. In patients undergoing percutaneous coronary intervention (PCI), the prognostic value of preprocedural total adiponectin is unknown. The present study was designed to address this issue.
Methods: From March 2006 to September 2007, pre-procedural total adiponectin levels were measured in 477 consecutive patients who underwent PCI for a median follow-up of 3.7 years. Patients presenting with acute ST-elevation myocardial infarction (STEMI) were excluded. The primary endpoint was the composite of death, non-fatal MI or stroke. Target lesion revascularization (TLR) was also examined.
Results: Median adiponectin level was 17±12 μg/ml [25-75th percentile: 13-21 μg/ml]. The primary endpoint occurred in 76 patients (15.9%). TLR was undertaken in 25 patients (9.2%). Female gender, higher HDL cholesterol and BMI lower than 25 were independent determinants of high adiponectin levels and lack of pre-treatment with beta-blockers were independently associated with high adiponectin level. In univariate analysis, adiponectin had a significant positive relationship (p=0.002) with the primary endpoint. In multivariate analysis, diabetes mellitus, lower creatinine clearance, high CRP and high adiponectin levels (hazard ratio=1.05 [95% CI: 1.01-1.09; p=0.006]) were associated with the primary endpoint. When patients were divided into tertiles according to adiponectin levels, patients in the upper tertile (≥30.2 μg/ml) had twice more risk of death, MI or stroke as compared to patients in the lowest tertile (<15.1 μg/ml) (Figure). No association was found between adiponectin levels and TLR (p=0.64).
Conclusions: In contrast to studies in the general population, high pre-procedural total adiponectin levels may be associated with increased risk of mortality, MI or stroke in patients undergoing PCI.

P4783 Prognostic significance of body mass index for in-hospital and long-term mortality in patients undergoing primary percutaneous coronary intervention
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Purpose: Prognostic significance of body mass index for in-hospital and long-term mortality in underweight and overweight population with ST elevation myocardial infarction (STEMI) is well-defined. However, cause of this relation has not well understood yet.
Method: 2007 patients in 36 months period admitted to our hospital emergency service within first 12 hours of chest pain and undergone primary percutaneous coronary intervention (p-PCI) were our study population. Patients were divided in four groups according to body mass index, <18.5 (n=182), 18.5 – 24.9 (n=732), 25 – 29.9 (n=768), 30 – 32.5 (n=325).
Results: Advanced age, anemia, renal functional impairment and nonspecific inflammation (baseline C-reactive protein) were more common in underweight group. Final TIMI 3 flow was lowest in underweight group and highest in overweight group (82.9% vs 89.9% vs 90.9% vs 90.5%, p<0.038, respectively). In-hospital mortality was lowest in obese group (6.0% vs 5.3% vs 3.1% vs 2.5%, p=0.034, respectively) and one-year mortality was highest in underweight group (13.5% vs 9.5% vs 6.7% vs 7.8%, p=0.038, respectively). After adjusting for potential confounding variables by Cox proportional hazard model, BMI was not a independent predictor for one-year mortality (Hazard ratio 0.98, 95% confidence interval 0.92 – 1.06, p=0.76).
Conclusion: While underweight is associated in-hospital and one year mortality in STEMI patients undergone p-PCI, body mass index is not a independent predictor for in-hospital and 1-year mortality. This can be explained by multiple comorbidities in underweight group and younger age, more aggressive treatment in overweight group.
Comparison on 1-Year MACE of everolimus-eluting stent Xience vs sirolimus-eluting stent cypher in diabetic patients

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Background: To expand the paucity of data on the efficacy of sirolimus-eluting stents (Cypher, Cordis, Bridgewater, NJ) vs everolimus-eluting stent Xience (Abbot Vascular, Redwood City, CA) in diabetic patients.

Methods: Due to Tuscany Region Medical Authority, Cypher stent was no more available after December 2008 and replaced by Xience stent. We collected the data of all-cause type 2 diabetic patients presenting with de novo or in-stent restenosis lesions in native coronary arteries treated in our institution from January 2003 to November 2008 (Cypher period) and from December 2008 to May 2010 (Xience period). The primary end point was the 1-year composite of major adverse cardiac events (MACE), including cardiac death, myocardial infarction (MI), and clinically driven target vessel revascularization (TLR).

Results: During the study periods, 440 lesions in 256 patients were treated with Cypher stent and 420 lesions in 212 patients with Xience stent (p=0.2). There were no significant differences among the two study groups except for previous myocardial surgical revascularization (8.6% in Cypher group vs 4% in Xience group, p=0.03) and stent length (22.4±8.7 vs 20.3±8.7 respectively, p=0.004). MACE-free survival was 89% in the Cypher group and 88% in the Xience group (p=0.7). Cardiac death occurred in 3 (1.2%) Cypher vs 4 (1.9%) Xience patients (p=0.7), MI in 4 (1.9%) vs 4 (1.9%) respectively, TLR in 37/440 (8%) Cypher vs 25/420 (6%) Xience lesions (p=0.2). Stent Thrombosis (ST) confirmed by angiography occurred in 2 (0.8%) Cypher vs 1 (0.5%) Xience patients (p=0.7).

Conclusions: The present study suggests that in diabetic patients, the Cypher stent is associated with a similar 1-year MACE rate when compared with Xience stent. Longer follow-up will evaluate the impact of the two stent in the occurrence of ST.

EPC capture stent and CD34+ mobilization in acute myocardial infarction

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Background: Percutaneous revascularization is the gold standard for the treatment of acute myocardial infarction (AMI), with the main limitation of in-stent restenosis for BMS and late stent thrombosis (ST) for both BMS and DES. Endothelial progenitor cells (EPC) CD34+ capture stents, promoting vascular healing, may be advantageous in preventing ST. The role of EPC on restenosis and atheromasic disease progression is unclear. The aim of the study is to evaluate the outcomes of AMI patients treated with EPC CD34+ capture stent and describe the mobilization kinetics of CD34+ and their clinical correlation.

Methods: 50 AMI patients underwent primary PCI with EPC CD34+ capture stent. Serial assays of CD34+ were performed by flow-cytometric analysis. Primary outcome was occurrence of death, myocardial infarction (MI), target vessel revascularization (TVR), target lesion revascularization (TLR), stent thrombosis, and major adverse cardiac events (MACE).

Results: Procedural success rate was 100%. At six months follow-up cardiac death, MI, TLR and TVR occurred respectively in 2%, 4%, 10% and 12% of patients. No case of ST was observed. The MACE-free survival was 82%. The mean peak value of plasmatic CD34+ was 4.69±3.76 cells/μl. A positive correlation was found between CD34+ concentration, age and infarct area. No correlation was detected between CD34+ concentration and occurrence of TVR, TLR and MACE.

Conclusions: EPC capture stent implantation seems to be safe and effective in the clinical setting of AMI, representing a possible alternative to BMS and DES. CD34+ cells plasmatic concentration seems not to correlate to coronary restenosis and atheromasic disease progression.

Developments in the last ten years - LHC and PCI

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Background: In 1996 German Cardiologists in Private Practice started to collect all their diagnostic procedures (LHC) and interventions (PCI) in a quality assurance registry. With only eight cath-labs in 1996 participants in the registry increased to 127 in 2010. We report changes since the beginning and compare the results of 2010 to the ones of the year 2000.

Methods: A quality based dataset is defined to enable a computer supported data collection. After each annual quarter a single center statistic and a benchmark comparison is reflected to the cath-labs. The registry allows conclusions about invasive cardiac care in Germany.

Conclusion: More patients were diagnosed and treated in 2010, who were older and in worse condition (ACS). The stent rate has increased and most of the procedures are performed ad hoc, there has been a trend in decision making from heart surgery to PCI.

Multivessel versus culprit lesion percutaneous coronary intervention in STElevation myocardial infarction: is more worse?

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Introduction: Existing data on the benefits of multivessel versus culprit lesion PCI during acute STElevation myocardial infarction (STEMI) are conflicting.

Methods: We compared outcomes between STEMI patients with multivessel disease treated with multivessel PCI versus those treated with culprit lesion only PCI who were enrolled in the national AMIS Plus registry of Switzerland from 2005 to 2011. Baseline characteristics of these groups were assessed using Student t-tests and chi-squared tests while multivariable logistic regression models were used to evaluate differences in in-hospital outcomes.

Results: From 11,069 STEMI patients who presented during this study period, we identified 4559 patients (41%) with multivessel disease (including 5.6% with main stem) who underwent PCI. Among these, 3541 patients (78%) were treated with culprit lesion PCI only while 1018 patients (4.7%; p<0.001) underwent ad hoc treated with multivessel PCI during their STEMI. Patients who underwent multivessel PCI had higher rates of cardiopulmonary resuscitation prior to admission (8.3% versus 5.8%; p=0.007) and Killip class ≥2 (12.0% versus 5.9%; p<0.001). Immediately after PCI, patients treated with multivessel PCI with nearly double the rate of cardiogenic shock (7.5% versus 4.7%; p<0.001) and in-hospital mortality (7.4% versus 4.4% p<0.001) compared to the patients treated with culprit PCI only. However, after adjusting for age, gender, Killip class and co-morbidities, the risk of in-hospital mortality after multivessel PCI was similar in both groups (adjusted odds ratio 1.28; 95% CI 0.92-1.79; p=0.14).

Conclusion: STEMI patients with multivessel disease who undergo multivessel PCI are sicker than those who undergo culprit lesion PCI only. After multivariable adjustment, multivessel PCI was not independently associated with worse in-hospital mortality.
Impact of successful thrombus retrieval during primary percutaneous coronary intervention with thrombus aspiration on the infarct size and microvascular obstruction: a magnetic resonance imaging study

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Background: Thrombosis (TA) during primary percutaneous intervention (PCI) is effective in opening the infarct-related artery in patients with ST-segment elevation myocardial infarction (STEMI), leading to better reperfusion and improved outcome. However, the effect of positive macroscopic efficiency of TA remains unknown. We aimed to evaluate the impact of positive thrombus retrieval during primary PCI with manual TA on infarct size (IS) and microvascular obstruction (MVO) as assessed by contrast-enhanced magnetic resonance imaging (CE-MRI) in a subset of patients with STEMI.

Methods: Inclusion criteria were patients aged <75 years, with first STEMI referred for PCI within 12 hours of onset of symptoms, infarct-related artery ≥2.5 mm in diameter, thrombus score ≥3 and no prior history of coronary disease. All patients underwent TA before stenting and were categorized according to positive or negative TA. Clinical and procedural characteristics of the study population were assessed, and CE-MRI was performed at 5 days and 6-months to evaluate MVO and IS.

Results: 88 patients were enrolled, mean age 55±10 years; 43.1% in the positive TA group. In the positive TA group, patients had higher 90-min total ischemic time, ST-segment resolution, post-procedural TIMI flow grade and persistent microvascular blush grade, and peak troponin did not differ significantly between groups. Independent predictors of final IS were: positive TA (OR 0.34, 95%CI 0.30-0.71), MVO (OR 1.75, 95%CI 1.28-0.71) and IS at 5 days (OR 2.06, 95%CI 1.87-3.32).

Conclusions: Positive thrombus retrieval during primary PCI with manual TA in STEMI reduces MVO and IS at 5 days and 6 months and represents a powerful predictor of final infarct size.

P4790 Intra-procedural stent thrombosis: a new risk factor for adverse outcome in percutaneous coronary intervention for acute coronary syndrome

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Background: Stent thrombosis (ST) is a rare complication of percutaneous coronary intervention (PCI). It is more common in the setting of acute coronary syndromes (ACS). It is not known whether intra-procedural ST (IPST) carries the same prognosis as post-procedural ST.

Objective: To examine the incidence, correlates and consequences of IPST.

Methods: We combined two large ACS studies – ACUITY and HORIZONS AMI. The angiograms were independently reviewed frame-by-frame for the occurrence of IPST. Patients with and without IPST were compared with respect to clinical and angiographic characteristics, and adjudicated events at 30 days and 1 year.

Results: Among 6,591 patients, there were 47 cases of IPST (49 lesions, 0.7%). There were no important differences in baseline characteristics between the two groups. Patients with IPST had significantly more often following bifurcation lesions treated, TIMI flow grade and persistent microvascular blush grade, and peak troponin did not differ significantly between groups. Independent predictors of final IS were: positive TA (OR 0.34, 95%CI 0.30-0.71), MVO (OR 1.75, 95%CI 1.28-0.71) and IS at 5 days (OR 2.06, 95%CI 1.87-3.32).

Conclusions: IPST is a rare complication of PCI in ACS, correlated with procedural factors. It is associated with an increased incidence of ST particularly in first 30 days and is an independent predictor of cardiac death at 1 year. IPST should be added as a distinct category of ST.

P4789 Real-world use of the second-generation cobalt-chromium sirolimus-eluting stent (CoCr-SES): 12-month results from the prospective multicentre FOCUS registry

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Background: The second-generation Firebird-2 cobalt-chromium alloy sirolimus-eluting stent (CoCr-SES) has been widely used in the world. The FOCUS registry is a prospective, international, and web-based program designed to collect clinical outcome data from real-world patients receiving the CoCr-SES.

Methods: From March 2009 through February 2010, a total of 5,084 patients from 83 clinical centers in 3 Asian countries eligible to receive a Firebird-2 CoCr-SES were enrolled in the FOCUS registry. Baseline characteristics and procedure patterns were collected and clinical follow-up is available for 1 year. The primary endpoint was the major adverse cardiac events (MACE, defined as the composite of cardiac death, non-fatal myocardial infarction (MI), and target vessel revascularization (TVR)) rate related to the CoCr-SES at 12-month follow-up.

Results: One year data were available for 5,013 (98.6%) of the 5,084 patients enrolled. The primary endpoint, MACE at 12 month follow-up, occurred in 174 (3.47%) of 5,013 patients, consisting of 43 (0.86%) cardiac death, 132 (2.63%) non-fatal MI, 88 (1.75%) cardiac death or non-fatal MI, and 15 (0.30%) target vessel revascularization. Secondary endpoints were: death, MI + TVR, death, MI or TVR, and death, MI or TVR.

Conclusions: The second-generation CoCr-SES was associated with low rates of 12-month MACE and ST in a broad spectrum of patients, thereby confirming the clinical safety and efficacy of this stent in a real-world setting. (FOCUS Registry: NCT00868829)

P4791 Polymer-Free Sirolimus- Versus Polymer-Based Paclitaxel-eluting stents. An individual patient data analysis of randomized trials

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Aims: The efficacy of polymer-free sirolimus-eluting stents (PF-SES) and polymer-based paclitaxel-eluting stents (PF-PES) was recently debated, mainly in high-risk subsets. We investigate outcomes of PF-SES versus PB-PES with an individual patient data analysis of randomized trials.

Methods: Patient data of the randomized prospective Stenting and Angiographic Restenosis - Test Equivalence Between 2 Drug-Eluting Stents (ISAR-TEST) and LIPSIA Yukon trials were pooled. Primary endpoint was in-stent late lumen loss (LLL) at 6-9 month angiography. Secondary endpoints were: death or myocardial infarction (MI), cardiac death or MI, target lesion revascularization (TLR) and MI. Interaction of treatment effect with subgroups (gender, age, insulin/non insulin treated diabetes, stable/unstable presentation and small/large vessels) was addressed.

Results: A total of 686 patients (PF-SES, n= 345 versus PB-PES, n= 341; diabetes 55.9% versus 51.0%, p= 0.19) and 751 lesions (PF-SES, n= 383 versus PB-PES, n= 368; B2 type 62.6% versus 62.1%, p= 0.15) were included. Control angiography (606 lesions) showed comparable in-stent LLL for PF-SES versus PB-PES (0.53±0.59 mm versus 0.46±0.57 mm, p= 0.15). Clinical follow-up (mean 20.4 months) confirmed no significant differences between PF-SES versus PB-PES regarding death or MI (12.4% versus 12.6%, Relative Risk: RR [95% Confidence intervals]= 1.17 [0.49-2.80]; p= 0.71), cardiac death or MI (10.7% versus 9.0%, RR= 1.17 [0.72-1.89]; p= 0.50); TLR (13.6% versus 13.7%, RR= 0.98 [0.65-1.47]; p= 0.93) and MI risk (5.7% versus 3.2%, RR= 1.79 [0.85-3.76]; p= 0.12) without treatment-effect modification among subgroups.

Conclusions: Polymer-free SES is comparable to polymer-based PES with respect to angiographic and clinical efficacy. No difference exists among gender, age, clinical presentation, insulin/non insulin treated diabetes and vessel diameter subgroups.
Lack of gender difference and improved in-hospital mortality rates in patients with cardiogenic shock following primary percutaneous coronary intervention: a UK tertiary cardiac centre registry study

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Background: Despite substantial recent improvement in mortality from cardiovascual disease, due primarily to success of primary and secondary prevention strategies, it remains the leading cause of death in the developed world. Among those patients hospitalized with acute myocardial infarction (AMI), cardiogenic shock (CS) is the foremost cause of death complicating up to 10% of admissions. Introduction of early revascularisation strategies and mechanical ventricular support have seen short-term mortality due to CS fall from 70-80% in the 1970s to around 50-60% in the 1990s. Previous studies suggest that women experience more CS than men (11.6% vs. 8.3%) in the setting of ST elevation MI. Whether primary percutaneous coronary intervention (PCI) for AMI has resulted in further reduction in in-hospital mortality and whether there are gender differences in outcomes due to CS is not known.

Aims: The aim of this study is to determine the rate of in-hospital mortality following primary PCI in the setting of CS and examine the gender differences in the incidence of CS and the rate of in-hospital mortality.

Methods: Data were collected prospectively among all patients presenting with AMI to a large UK tertiary cardiac centre and undergoing PCI between April 2008 and October 2011.

Results: In total 2866 patients (male: 2023 [70.6%] vs. female: 843 [29.4%]) underwent PCI. In total, 141/2866 (4.9%) had percutaneous coronary procedures (balloon angioplasty only or stenting) in the setting of cardiogenic shock. There were 81/2023 (4%) male patients and 60/843 (7.1%) female patients with CS undergoing PCI. There were no significant differences in the baseline characteristics between male and female patients except female patients were older than male (mean age 64.1 years vs. female 69.9 years, p<0.004). The overall unadjusted in-hospital mortality rate was 35.4% with no difference in the genders (male: 35.8% vs. female: 35%, p=0.730).

Conclusion: The present analysis demonstrates that in the PCI era, there is a reduction in the incidence of cardiogenic shock with reduced unadjusted in-hospital mortality rates following primary PCI. The unadjusted in-hospital mortality rates did not differ between the genders despite the fact that there were more women that had presented with cardiogenic shock.

Twelve-month safety and performance results of the paclitaxel-eluting bioabsorbable magnesium scaffold in the prospective, multicenter first-in-man trial - BIOSOLVE-I

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Purpose: Absorbable metal scaffolds (AMS) are developed to overcome limitations of current permanent bare or drug-eluting coronary stents like stent thrombosis despite prolonged dual antiplatelet therapy (DAPT), caged vessel segment not allowing vasoconstriction and remodeling or chronic vessel wall inflammation. Magnesium is an essential element of the human body, thus Magnesium is considered as a potential alloy for aspiration. To overcome the limitations associated with the first generation of a bare AMS a Drug (Paclitaxel) Eluting Absorbable Magnesium Scaffold was developed (DREAMS).

Methods: Between July and December 2010, 46 subjects were enrolled in the first-in-man BIOSOLVE-I study, and assigned to two different cohorts with different follow-up schedules. Clinical follow-up for both cohorts is scheduled at 1, 6, 12, 24 and 36 months. angiographic follow-up for cohort 1 at 6 months and for cohort 2 at 12 months. Angiographic assessment was performed by an independent, core laboratory. The primary endpoint is Target Lesion Failure (TLF), defined as the composite of cardiac death, target vessel myocardial infarction and clinically driven target lesion revascularization at 12 months of follow-up. Results: Of the 46 subjects 34 were male and 12 were female subjects with a mean age of 65.3±9.7 years ranging from 42 to 80 years. Hyperlipidemia (89%), hypertension (87%) and history of myocardial infarction (33%) were the major medical risk factors. Type A (23.5%), Type B1 (9.1%) and Type B2 (6.8%) lesions were treated with a 3.25/16 mm (49.8%) or a 3.5/16 mm (51.1%) DREAMS. The target lesion failure rate at 12-month is 7.0% with no cardiac death, one periprocedural target vessel non-Q wave myocardial infarction and two clinically driven target lesion revascularizations (TLR). There was no scaffold thrombosis. The angiographic results of 33 patients consenting for the 12-month follow-up will be available upon presentation.

Conclusion: DREAMS showed an excellent safety profile and a low TLF rate up to one year follow-up.

In hospital clinical outcome of patients with definite stent thrombosis

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Background: The outcome of patients with angiographically proven stent thrombosis is only insufficiently known. We sought to evaluate presentation and outcome of patients with angiographically proven stent thrombosis.

Methods: 76 consecutive patients (mean age 69±12 years: 53 male with 61 angiographically proven stent thrombosis between 2003 and 2010 were included in the analysis. The time interval between initial stent implantation, rate of dual antiplatelet therapy prior to presentation and presentation with stent thrombosis, frequency of death during hospitalisation, predictors of death as well as frequency of recurrent stent thrombosis were evaluated.

Results: In 30 patients (40%) had early ST, 3 patients (4%) had late ST and 12 patients (16%) had late ST 3 patients (78%) were on dual antiplatelet therapy at the time of stent thrombosis. 60 patients (79%) presented with STEMI while 16 patients (21%) presented with other forms of acute coronary syndrome. 13 patients (17%) died during hospitalization. Univariate predictors of death were presentation with cardiogenic shock (OR 1.61, 95% CI 1.32-1.97, p<0.001), LV ejection fraction <30% at presentation (OR 1.37, 95% CI 1.07-1.73, p=0.010), and discontinuation of clopidogrel administration at presentation (OR 1.35, 95% CI 1.06-1.71, p=0.010). Cardiogenic shock (OR 1.46, 95% CI 1.24-1.72, p=0.001) and discontinuation of clopidogrel administration (OR 1.22, 95% CI 1.04 – 1.43, p=0.020) remained independent predictors of death during hospitalization. 5 patients (7%) had recurrent ST during hospitalization.

Conclusion: Stent thrombosis is associated with a detrimental acute prognosis with severe systolic left ventricular dysfunction (EF <30%), cardiogenic shock and discontinuation of clopidogrel being predictors of death. Recurrent stent thrombosis is not uncommon.

Cost-effectiveness of drug-coated balloon angioplasty and drug-eluting stent implantation for treatment of coronary in-stent restenosis

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Purpose: In-stent restenosis (ISR) is a persistent problem limiting the long-term success of percutaneous coronary intervention. Recent studies have demonstrated safety and efficacy of drug-coated balloon (DCB) angioplasty for the treatment of coronary ISR. The cost-effectiveness of this procedure is unknown.

Methods: A Markov state-transition decision analytic model was used to assess the comparative cost-effectiveness of two common treatment strategies for BMS-ISR: stenting with paclitaxel-eluting DES versus paclitaxel-coated balloon angioplasty (SeQuent Please, B. Braun Melsungen AG, Berlin, Germany). The model accounted for varying procedural efficacy rates, complication rates, and cost estimates. Data on procedural outcomes associated with both treatment strategies were derived from the literature, and the cost analysis was conducted from a health care payer perspective. Effectiveness was expressed as life-years gained.

Conclusion: Cost-effectiveness was calculated by dividing the difference in mean costs (costs of DCB angioplasty – costs for DES implantation) by the difference in effective life expectancy in the DCB arm – life expectancy in the DES arm. All simulations were performed using Monte Carlo simulations with 100,000 random trials.

Results: In the base-case analysis, initial procedural costs were €1,300.38 for DCB angioplasty and to €3,309.66 for DES implantation. Over a 12-month time horizon, the DCB strategy was found to be less costly (€1.300.38 versus €3,305.30) and slightly more effective in terms of life expectancy gained (0.983 versus 0.976 years) than the DES strategy. Extensive sensitivity analyses indicated that, in comparison with DES implantation, the cost advantage of the DCB strategy was robust to clinically plausible variations in the values of key model input parameters. The variables with the greatest impact on base case results were the duration of dual antiplatelet therapy with acetylsalicylic acid and clopidogrel after DCB angioplasty, the use of generic clopidogrel, and variations in the costs associated with the DCB device.

Conclusion: DCB angioplasty is a cost-effective treatment option for coronary BMS-ISR. The higher initial costs of DCB are more than offset by later cost savings, predominantly as a result of reduced medication costs. Health care payers
would benefit from a wider adoption of this technology, as DCA angioplasty can be regarded as one of the rare innovative medical interventions that are cost-saving at equal or even increased effectiveness.

### P4796

Differential of vascular response between everolimus- and paclitaxel-eluting stents for small coronary artery diseases: optical coherence tomography analysis

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**Background:** The aim of this study is to evaluate the differences of chronic vascular response following small coronary stenting between everolimus-eluting stent (EES) and paclitaxel-eluting stent (PES) evaluated by optical coherence tomography (OCT).

**Methods:** SACRA and PLUM registries are prospective, multicenter registry to assess the efficacy of single paclitaxel- (PES) or everolimus-eluting stents (EES) in patients with small coronary artery diseases. Inclusion criteria of both registries were

1. Significant stenosis in vessels <2.5 mm in reference diameter, 2. lesion length <30 mm.

From these two registries (506 patients with 533 lesions), non-restenotic 50 EESs and 50 PESs were imaged with OCT at 9-month follow-up and analyzed at interval of 1 mm.

**Results:** Average intimal hyperplasia thickness was not different between the two groups. Exposed struts and layered intima were observed more frequently in PES group than EES group.

<table>
<thead>
<tr>
<th>OCT results</th>
<th>EES</th>
<th>PES</th>
<th>p</th>
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<tbody>
<tr>
<td>No. of stent</td>
<td>50</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>No. of observed cross-sections</td>
<td>859</td>
<td>625</td>
<td></td>
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<tr>
<td>Homogeneous intima</td>
<td>800 (99.3%)</td>
<td>737 (99%)</td>
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<tr>
<td>Heterogeneous intima</td>
<td>38 (4.4%)</td>
<td>28 (3.4%)</td>
<td>0.31</td>
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<tr>
<td>Layered intima</td>
<td>18 (2.1%)</td>
<td>60 (7.3%)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Peri-stent ulcer like appearance</td>
<td>30 (3.5%)</td>
<td>103 (12.5%)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Peri-stent ulcer size appearance</td>
<td>53 (6.2%)</td>
<td>106 (12.8%)</td>
<td>&lt;0.0001</td>
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<tr>
<td>No. of analysis strut</td>
<td>3900</td>
<td>7605</td>
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<tr>
<td>Exposed strut</td>
<td>26 (0.27%)</td>
<td>130 (1.67%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Malapposed strut</td>
<td>9 (10.9%)</td>
<td>22 (0.17%)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Percent neointimal hyperplasia area, %</td>
<td>20.4±6.6</td>
<td>22.0±10.7</td>
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<tr>
<td>Average NIT, μm</td>
<td>0.14±0.06</td>
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<tr>
<td>Maximum NIT, μm</td>
<td>0.02±0.08</td>
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<tr>
<td>Minimum NIT, μm</td>
<td>0.07±0.04</td>
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<td>Maximum NIT/ Minimum NIT, μm</td>
<td>0.15±0.04</td>
<td>0.21±0.09</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Conclusions: This study suggested that characteristics of neointimal hyperplasia after EES implantation were more stable compared with PES although neointimal growth was similar between the two groups.

### P4798

Second vs. first generation DES are associated with a better safety profile in real world coronary percutaneous intervention: analysis of 3266 procedures from a single centre prospective registry

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**Background and Aims:** When compared to their first generation counterparts, second generation DES have been associated with better clinical outcomes in recent RCTs, which, together with safety concerns (mostly stent thrombosis [ST]), led to a progressive abandoning of the latter in most clinical settings. Our goal was to assess whether or not newer devices translate into higher safety in a real world population. For that purpose, our main outcome measure was the occurrence of definite ST.

**Methods and Results:** Between January 2003 and December 2009, 3266 patients (pts) who were submitted to PCI with at least one DES. Of these, 2260 (69.2%) who were treated with first generation (1stGEN) DES only [Sirolimus=1178 (36.1%) and P D-200 (909 (28.4%)] patients, and 1006 (30.8%) with second generation (2ndGEN) DES only. Patient, angiographic and procedural characteristics were prospectively recorded in a dedicated data base; study groups differed in age (63±10.9 years vs. 65±11.2 years; p<0.001), prevalence of hypertension (72.6% vs. 77.1%; p=0.006), smoking (50.3% vs. 44.6%; p=0.003), prior ACS (17.1% vs. 12.4%; p<0.001), ACS presentation (40.8% vs. 49.7% p<0.001) and Syntax score (14±10.3 vs. 13±9.8; p=0.04). ARC-defined definite ST occurred in 75 (2.3%) pts during a median follow-up of 598 days (IQR range 453; 1206), 715 (IQR 463; 1546) for 1stGEN vs. 508 (IQR 440; 720) for 2ndGEN (p<0.001). In order to account for differences in follow-up duration, only adjudicated events occurring during the first year were included in the per-procedure analysis (n=70; 1.3%).

After correcting for clinical differences and the Syntax Score, the use of 1stGEN DES was associated with a significant 2.3 fold increase in the risk of definite ST (95% CI 1.02-5.12; p=0.046) and implantation of paclitaxel-DES only (but not sirolimus-DES) was an independent predictor of the occurrence of definite ST (corrected HR 1.8; 95% CI 1.01-3.34; p=0.047). Although slightly numerically superior in patients treated with 1stGEN DES (3.5% vs. 3.4%), total mortality was not statistically different between groups (HR 1.16; 95 CI 0.77-1.74; p=0.48).

**Conclusions:** Our data suggests that in the real world clinical practice, the use of first generation DES should be restricted to very specific subsets of patients with ACS, and that newer devices actually appear to exhibit a better safety profile when broadly used for PCI with DES.

### P4799

Impact of adjunctive post-dilatation after drug-eluting stent implantation on the clinical outcomes in patients with acute myocardial infarction: Sub-study of EVER-ZOTA multicenter trial

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**Backgrounds:** Although drug-eluting stents (DES) are more effective than bare-metal stents (BMS) in preventing coronary restenosis, stent underexpansion was known to be an important predictor of early stent thrombosis and restenosis in the DES era. Recently, a large retrospective study demonstrated that post-dilatation after DES implantation reduced the restenosis rate. However, the population of the study did not include patients with acute myocardial infarction (AMI). The aim of present sub-study of EVER-ZOTA multicenter trial was to evaluate the impact of an adjunctive post-dilatation after DES implantation on the clinical outcomes in patients with AMI.

**Methods:** We studied 474 (343 men, 65±12 years old) patients who underwent DES implantation for AMI including 368 with postdilatation (235 male, 66±12 years old) and 116 with under-dilatation (90 male, 63±12 years old). Rate of cumulative 12-month events, such as cardiac death, target-vessel related MI, revascularization, or stent thrombosis were compared between groups.

**Results:** Compared with the postdilatation group, the un-postdilatation group had younger, less calcified lesion, and obtained postprocedural TIMI-3 flow. They had also significantly better on composite events in 12 months (5.6% vs. 9.9%, p<0.045) (Figure). However, Cox regression survival analysis showed the Killip Class ≥ 3 (odd ratio 17.271, 95% CI 5.433-54.906, p<0.001) and age (odd ratio 1.061, 95% CI 1.005-1.119, p<0.031) to be independent predictors of 12-month composite events rather than postdilatation itself.

**Conclusion:** Postdilatation after DES implantation in patients with AMI does not seem to have a benefit on the 12-month clinical outcomes. Age and Killip Class rather than postdilatation itself would be more predictive of 12-month clinical outcomes.

### P4800

Bare-nitroelast stent versus paclitaxel-coated balloon for femoropopliteal revascularization. An adjusted indirect comparison meta-analysis of randomized trials

S. Cassese, R.A. Byrne, I. Ott, T. Ibrahim, T. Tada, L. King, A. Kastrati, M. Fusaro. German Heart Center, Clinic for Heart and Circulatory Diseases, Munich, Germany

**Aims:** In femoropopliteal artery (FPA) disease, Bare-Nitroelast Stent (BNS) and Paclitaxel-coated balloon (PCB) improved outcomes as compared to Uncoated-Balloon (UCB) angioplasty. Nevertheless, the relative efficacy of BNS vs. PCB remains unknown, due to the lack of head-to-head comparisons. We performed an adjusted indirect comparison meta-analysis of randomized trials to evaluate outcomes of BNS versus PCB in FPA disease.
P4801 Bivalirudin Vs Unfractionated Heparin during Percutaneous Coronary Intervention in High Risk Patients for Bleeding, AntiCoagulant Regimen In high risk Patients for Bleeding - ACRIPAB Trial

A. Feldman, K. Suleiman, L. Bushari, E. Rozner, N.A. Freedberg, Y. Turgeman, Haemek Medical Center, Afula, Israel

Introduction: In low to medium risk population undergoing PCI Bivalirudin (BIV) exhibited significantly lower rate of bleeding compared to unfractionated heparin (UFH). However, clinical outcome and bleeding complications in high risk population was not established yet.

Aim: Randomized double blinded prospective trial comparing efficacy and safety of BIV vs. UFH on top of dual antiplatelet therapy during PCI among patients with NSTEMI or angiography with high risk for bleeding.

Methods: There were 100 consecutive patients (66.6±12.3 years old, 69% males) enrolled in our study with 1:1 distribution between BIV and UFH groups. With starting of PCI BIV or UFH were administrated in acceptable doses. The study end points were: major, minor bleeding, port of entry complications, MACE in hospital and after 30 days follow up.

Baseline characteristics: There were 87% patients with diabetes mellitus, 98% with hypertension, 22% with chronic renal failure, 30% older than 75 years, 21% with haemoglobin plasma level <11 mg/dl and 58% with systolic blood pressure >180 mm Hg. 24% of participants were catheterized due to NSTEMI. Femoral arterial puncture was performed in 73% of patients with haemoglobin plasma level <10 mg/dl.

Results: Median FU was 11.5 months. Angioplasty with BNS was found inferior to PCB with regard to TLR (OR= 2.60 [1.27–5.32], z= 2.63, p=0.008), with a trend toward higher binary restenosis (OR= 2.03 [0.99–4.18], z= 1.93, p= 0.052). No significance in mortality was evident among study groups (OR= 1.79 [0.37–8.55], z= 0.73, p=0.46). BNS vs. PCB comparison.

Conclusions: In diseases of femoro-popliteal artery, PCB offers superior freedom from repeat revascularization as compared to BNS. Both revascularization strategies appeared safe. Adequately powered, randomized, head-to-head comparisons are needed.

MANAGEMENT OF CORONARY ARTERY DISEASE AND PERCUTANEOUS CORONARY INTERVENTION COMPLICATIONS

P4802 Triple over Dual anti-Platelet therapy was not mandatory in Acute Coronary Syndrome Patients with 2nd Generation Drug eluting Stent Implantation


Purpose: Triple antiplatelet therapy with clopidogrel has been known to be superior to dual antiplatelet therapy in the era of 1st generation DES in terms of clinical outcome. However, it remains to be cleared whether triple antiplatelet therapy also has clinical significance after implantation of 2nd generation DES even in patients with acute coronary syndrome (ACS) Methods: In CO-ACT registry, the study subjects were 644 patients who underwent PCI with Everolimus eluting or Zotarolimus eluting stent (Endeavor, Xience V or Promus) with ACS were analyzed retrospectively. The patients were divided into 2 groups after propensity score matching: those treated with triple antiplatelet drugs (aspirin, clopidogrel, and cilostazol; group 1, n=208, M=61.16 (55.7%), mean age=60.7±14.6 years) and those with dual anti platelet drug treatment (aspirin and cilostazol; group 2, n=436, M=457 (63.9%), mean age=67.8±11.3 years). The incidences of various clinical outcomes were compared between two groups.

Results: The mean follow-up duration of group 2 was 17.6±6 month (median 13.4). There was no significant difference in the incidence of major bleeding between two groups. Compared with group 1, group 2 showed no significant difference of cardiac death and MI (OR, 1.12; 95% CI, 0.78–1.37; p=0.43), MACE (cardiac death, MI and TLR) (OR, 1.55; 95% CI, 0.77–1.85; p=0.03). Kaplan-Meier curves for MAC did not show any survival benefits in triple anti-platelet therapy.

Conclusions: Triple antiplatelet therapy has no beneficial effect in clinical outcome compared to dual antiplatelet therapy in patients with 2nd generation DES even in ACS patients.

P4803 Brain natriuretic peptide during coronary intervention prevents endothelial dysfunction post PCI via NP-cGMP activation

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Background: Percutaneous coronary intervention (PCI) is associated with endothelial dysfunction (ED) and systemic vascular injury induced by contrast media (CM). According to our previous study, brain natriuretic peptide (BNP) administration 24 hours post PCI decreases ED.

Aims: The purposes of this study: 1. To evaluate the ability of human BNP (hBNP) infusion during PCI to prevent ED in patients with acute coronary syndrome (ACS) post the PCI. 2. To investigate the effect of contrast medium (CM) administration on human coronary microvascular endothelial cells (HCMEC).

Methods and Results (in vivo): Eleven hundred and twelve non-ST elevation ACS who underwent PCI were randomized into 2 groups: a group who received hBNP infusion during the procedure (n=64), and another control group who received nirogycerin (n=67) according to standard protocol. The endpoints were: the rate of decreased flow mediated dilatation (FMD) (by ≥2.5%), the increase in BNP, serum creatinine (sCr) and decrease of estimate Glomerular Filtration Rate (eGFR), 24 hr after, compared to pre operative value. There was no significance difference in baseline FMD. The percent change of FMD was significantly reduced in the control group (p=0.05) but increased non-significantly in the hBNP group (p=0.16). FMD was significantly higher in the hBNP group (p=0.04). BNP, corin and sCr increased significantly in the control group (p=0.001, 0.003, 0.0002 respectively) but not in hBNP group (p=0.09, 0.07, 0.18). eGFR decreased significantly in the control group (p=0.002), no change in the hBNP group (p=0.4).

Methods and Results (in vitro): HCMEC were treated with CM (10%) in the presence and absence of BNP. eNOS, corin and cGMP levels were measured by ELISA and the results were compared to untreated cells. In both treatments eNOS was significantly reduced (p<0.001) and corin was significantly increased (p=0.002), to the same levels. cGMP was not affected by CM treatment (p=0.278), but was increased significantly (p<0.001) by BNP combination. cGMP immuno-fluorescence staining of HCMEC showed distorted cellular cGMP appearance by CM treatment, that was corrected in the combination with hBNP with accentuated subcellularaluminal staining.

Conclusions: These data show that CM reduces eNOS in endothelial cells and increases corin and cGMP. Therefore, reducing NO-cGMP pathway probably is the mechanism that induces ED in vivo. BNP treatment reduces FMD and kidney injury post PCI. A compensatory rise in corin that increases BNP as well the NO-cGMP pathway, maintains cytosolic cGMP via NP-cGMP, and compensates for NO-cGMP loss, which prevents ED.

P4804 Why is the posterior myocardial infarction the most frequent cause of acute mechanical complications?

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Background: The prevalence of ramus circumflexus (LCX) as an infarct related artery (IRA) in STEMI patient populations is low, around 10-15%. The prevalence of ramus circumflexus (LCX) and its branches as a culprit artery in published groups of AMI patients. To estimate the reason for low prevalence of LCX as IRA in patients with mechanical complications of AMI.

Objective: To estimate the reason for high involvement of LCX as IRA in patients with mechanical complication of AMI: To estimate the reason for low prevalence of LCX as IRA in published groups of AMI patients.

Methods: Registry of patients with acute coronary syndromes treated in the tertiary cardiac centre.

Results: In the group of 809 STEMI patients treated in period 2008-2011, the LCX, LAD, and RCA were detected as IRA in 133 (16%), 347 (43%) and 308 (38%) patients respectively. In the parallel group of 709 NSTE-ACS patients the proportion of LCX, LAD and RCA as IRA was 220 (31%), 322 (33%) and 209 (29.5%) respectively. The difference of LCX involvement in STEMI (16%) compared to NSTE-ACS patients (31%) was highly significant (p<0.001). From the group of 7 patients hospitalized for the acute mitral regurgitation due to rupture...
of papillary muscle the LCX was identified as IRA in 6 (86%) patients. The hospital mortality was 29%. In the group of 5 patients hospitalized with the rupture of free left ventricle wall post AMI, the LXC was culprit in 3 (60%) patients. The hospital mortality was 40%. None of the 9 patients received immediate reperfusion therapy for acute LXC occlusion as they all were initially identified and treated as NSTE-ACS.

Conclusions: In the present era of catheter based reperfusion therapy, the posterior AMI due to LCX occlusion is the most frequent cause of serious mechanical complication of AMI because of improper reperfusion treatment. The incorrect evaluation of patients with posterior AMI as beasting NSTE is also the cause of low prevalence of LCX as culprit in the groups of STEMI patients treated with immediate reperfusion therapy. We showed that about 30% of patients with acute LCX occlusion are not receiving needed timely reperfusion therapy.

**P4807**

Onset-to-needle times in patients with ST-segment elevation myocardial infarction: shortest referral route to a primary coronary intervention facility

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Introduction: Primary percutaneous coronary intervention (PCI) is the preferred therapeutic strategy for patients with acute ST-elevation myocardial infarction (STEMI). However, several referral routes between onset of symptoms and PCI exist namely: Pre-hospital diagnosis and direct transfer to PCI, emergency room visit and on-site transfer to PCI, or emergency room visit and secondary transfer to PCI. We compared the delays between onset and PCI associated with each referral route.

Method: Data was obtained in a retrospective analysis of randomly selected STEMI patients from 64 hospitals in France. For each patient, the referral route and onset-to-needle time was obtained. Onset-to-needle time was defined as time from onset of symptoms to time of arterial puncture for PCI. We used a Cox proportional-hazards model to compare delays between referral routes.

Results: In total, 1217 patients were included in the analysis. Median onset-to-needle time was 186 min (Q1: 133; Q3: 252) for the pre-hospital diagnosis route, 237 min (Q1: 165; Q3: 368) for the onsite transfer route and 305 min (Q1 230; Q3 570) for the secondary transfer route. There was no difference in median onset-to-needle times between hospital types or volume of activity. After adjusting for age, year of admission and history of cardiovascular disease, pre-hospital diagnosis was associated with the shortest delay as compared to onsite-transfer (Hazard ratio (HR) 0.71 [0.59 - 0.86]) and secondary transfer (HR 0.67 [0.52 - 0.86]).

Conclusion: Pre-hospital diagnosis with direct transfer to PCI leads to shorter delays in patient care. In France, this management pathway requires the presence of an emergency physician at first medical contact.

**P4808**

Improved prognosis of weekends/holidays admission for acute myocardial infarction and a decreasing weekend-effect from 2005 to 2010

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Purpose: Many hospitals provide routine care on weekdays and only emergency or urgent care on weekends. Accordingly, hospital staffing is reduced on weekends and this difference may result in different outcome in patients with acute intervention (PCI) involving bare-metal stents in pts with stable coronary artery disease (CAD). Our study compared drug-eluting stents (DES) PCI with optimal medical therapy (OMT) in pts with non-acute CAD.

Methods: In prospective cohort study 481 pts (mean age 59 yrs) with stable CAD on OMT (beta-blockers, statins, antiplatelets, ACE inhibitors) were included. In history (>2 months ago): acute coronary syndrome (ACS)<-80%, PCI>14.9%, coronary bypass<17.5%, stroke<9.6%, diabetes<18.5%. 302 of pts underwent PCI (PCI group) and 179 of pts continued on conservative therapy (medical-therapy group). The mean follow-up period in PCI and medical-therapy groups was 3.5±1.6 yrs and 5.4±1.3 yrs respectively. The primary outcome was the occurrence of major adverse cardiac and cerebrovascular events (MACE)=vascular death, ACS, stroke/transient ischemic attack. The composite endpoint included MACE and revascularization in any affected arterial area.

Results: Most of the demographic and clinical characteristics were similar in the two groups. PCI was performed for 1-, 2- and multivessel diseases in 57.3%, 30.5% and 9.3% respectively. 98% of PCI group received DES (Cypher and second generation of DES), the double antiplatelet therapy (DAPT) was ≥12 months in all pts. The total frequency of MACE in the PCI group was 4.8/100 pts/ys and 5.3/100 pts/ys in the medical-therapy group (RR for the PCI group 0.96[95% CI 0.61-1.5]). The frequency of composite endpoint was 7.3/100 pts/ys and 7.1/100 pts/ys respectively (RR for the PCI group 1.02[95%CI 0.7-1.3]).

Conclusion: Elective PCI with DES and optimal duration of DAPT don’t have advantages over optimal medical therapy in pts with CAD.
myocardial infarction (AMI). Implementation of national quality improvement program may have the potential to obliterate the "weekend-effect" in patients with AMI.

Methods: Between November 2005 and December 2010, 25,233 patients (18.025 men; mean age = 63.3±12.8 year-old) were included from Korea AMI Registry. Exposure was defined as admission on a Saturday, Sunday, or a holiday. The study population was stratified according to four time-periods: 2005.11.11 – 2006.12.31 (KAMIR I; n=7,077), 2007.11 – 2008.11.31 (n=1,319; KAMIR II; n=4,605), and 2008.12.1 – 2010.12.31 (Kormil; n=13,722).

Results: The proportions of weekend-admissions were 27.4%, 27.9%, and 28.2%, respectively. Patients admitted on weekend were younger and had more typical chest pain, inferior MI, ST-segment elevation MI, higher Killip class, and higher serum glucose, CK-MB, and triglyceride levels. Current smokers were more frequently observed in patients admitted on weekend. Cardiopulmonary resuscitation were more frequently performed in patients admitted on weekend. From KAMIR I 6.5% of patients admitted on weekends died compared to 5.2% of those admitted on weekdays (p<0.037). During the two following periods the apparent difference between weekends and weekdays diminished: KAMIR II (7.1% versus 7.8%, p=0.436) and Kormil (6.2% versus 5.8%, p=0.367). Accordingly, in the adjusted multivariate analysis an increased all-cause mortality in patients admitted on weekends was observed only in KAMIR I with a weekend-weekday hazard ratio (HR) of 1.320 (95%CI: 1.001-1.741, p=0.049) but was not found in KAMIR II (HR 0.945, 95% CI: 0.688-1.298, p=0.728) and Kormil (HR 0.904, 95% CI: 0.744-1.098, p=0.307).

Conclusions: We showed that a weekend-effect on mortality in patients with AMI has previously been present, but it has decreased over the past five years.

**P4809**

**Syntax score predicts major bleeding after drug-eluting stent implantation**


**Purpose:** The bleeding complication has been one of frequent complications in the drug-eluting stent (DES) era. Previous study reported that percutaneous coronary intervention (PCI) in complex lesion is an independent correlate of major bleeding. This finding may be explained by more complicated procedure and long-term anti-platelet therapy. The Syntax score is a current angiographic tool grading the complexity of coronary artery disease. The aim of this study was to assess the ability of the Syntax score to predict major bleeding after DES implantation.

**Methods:** We analyzed a consecutive 560 patients treated with DES in the all-comers population between January 2007 and January 2008. Endpoints were analyzed for major bleeding (defined according to the REPLACE-2 trial) and late stent thrombosis during 3 years. The Syntax score was assessed with angiogram before PCI by 2 cardiologists. Patients were stratified according to tertiles of the Syntax score: low score (0-12, n=179), intermediate score (13-24, n=220), and high score (25, n=168).

**Results:** Incidence of the major bleeding was seen in 49 patients (8.6%) during 3 years. There were 15 stent thrombosis (2.7%). The median Syntax score was 17 (range 0 to 79.5). Among patients in the low, intermediate, and high scores, the 3-year rate of major bleeding were 4.7%, 5.0%, and 16.5%, respectively (p<0.001). On univariate analysis, the Syntax score showed a strong association for each 10-unit increase in Syntax score, Odds ratio 69.69, 95% confidence interval 1.39-2.06, p=0.001. Multivariate logistic regression including clinical factors showed in the table.

Predictive factors of Major Bleeding

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syntax score (10-unit increase)</td>
<td>1.58</td>
<td>1.25-2.04</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>3.62</td>
<td>1.50-9.89</td>
</tr>
<tr>
<td>Age</td>
<td>1.68</td>
<td>1.09-2.57</td>
</tr>
</tbody>
</table>

Multivariate logistic regression model.

**Conclusions:** In the all-comers population undergoing DES implantation, the Syntax score has a predictive ability for patients at risk of major bleeding. The score was useful for clinical decision making regarding optimal duration of dual anti-platelet therapy after DES.

**P4811**

**Comparison of the new Mayo Clinic risk scores and clinical Syntax Score in predicting adverse cardiovascular outcomes following percutaneous coronary intervention at our heart center**

H.J. Brown, J. Ho Khe Sui, C. Tan. Philippine Heart Center, Quezon City, Philippines

**Background:** Risk stratification of patients who will undergo percutaneous coronary intervention (PCI) can help physicians and patients and their families understand the risks of the procedure, thus providing an objective basis for decision-making.

**Objective:** To compare the prognostic value of the Clinical Syntax Score (CSS) and New Mayo Clinic Risk Scores (NMCRS) for in-hospital and 30-day mortality and major adverse cardiovascular and cerebrovascular events (MACCE) following PCI at our center.

**Methods and Results:** The NMCRS for Predicting Mortality, NMCRS for Predicting MACE and CSS of all patients who underwent PCI from April 1, 2011 to September 30, 2011 were computed. Of the 482 patients included in the study, 22 (4.6%) died while 37 (7.7%) had the composite endpoint (mortality, MI, emergency CABG, CVA) during hospitalization. 30 days after PCI, 9 (2.0%) died while 19 (3.9%) had the composite endpoint. The prognostic value of the NMCRS for Predicting Mortality, NMCRS for Predicting MACE and CSS for in-hospital mortality, as measured by the c-statistic, is 0.827, 0.813, and 0.816 (P < 0.05 for all), respectively and for in-hospital composite endpoints is 0.791, 0.751, and 0.755 (P < 0.05 for all), respectively. 30 days after PCI, the prognostic value of the NMCRS for Predicting Mortality, NMCRS for Predicting MACE and CSS, as measured by c-statistic is 0.751 (P < 0.05), 0.760 (P < 0.05), and 0.651 (P = 0.121), respectively and for composite endpoints is 0.736 (P < 0.05), 0.763 (P < 0.05), and 0.621 (P = 0.10), respectively.

**Conclusion:** The NMCRS for Predicting Mortality has better prognostic utility for in-hospital mortality and composite endpoints while the NMCRS for Predicting MACE better predicts 30-day mortality and composite endpoints as compared to the CSS.

**P4812**

**Protamine usage following implantation drug-eluting stents: is it safe?**

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**Background:** Prompt reversal of heparin anticoagulation by protamine administration after coronary stent implantation could be an important therapeutic option. It could help the treatment of serious procedural complications such as vessel rupture or perforation or to allow immediate femoral artery sheath removal to avoid puncture site complications and decrease patient discomfort. However, this approach is rarely used after coronary drug eluting stent (DES) implantation because of the possible increased risk of stent thrombosis. ST is a rare event, so in order to be detected a large sample study is required.

**Methods:** We retrospectively analyzed the incidence of acute and subacute stent thrombosis in 6023 patients submitted to percutaneous coronary intervention who received 2945 drug eluting stent divided in 2 groups: GI with 2509 DES who
received protamine after procedure and GII with 436 DES who did not receive this drug.

Results: Six patients (0.24%) had subacute stent thrombosis in the group receiving protamine (299 DES) and only one patient (0.02%) in the group who did not receive this drug (436 DES) (p-value = 0.96; odds ratio: 0.96; 95% confidence limits).

Conclusion: Immediate reversal of heparin anticoagulation by protamine after coronary drug eluting stent implantation in our study was safe and did not predispose to stent thrombosis. This finding has important clinical consequences.

Impact of Mehran Risk Score for the prediction of Contrast-induced Nephropathy in the Japanese patients undergoing Percutaneous Coronary Intervention

Impact of Mehran Risk Score for the prediction of Contrast-induced Nephropathy in the Japanese patients undergoing Percutaneous Coronary Intervention

Table 1

<table>
<thead>
<tr>
<th>Mehran risk score</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Low</td>
<td>1.00 (reference)</td>
<td>0.0%</td>
</tr>
<tr>
<td>Medium</td>
<td>1.18 [0.83-1.65]</td>
<td>0.349</td>
</tr>
<tr>
<td>High</td>
<td>1.91 [1.21-2.94]</td>
<td>0.004</td>
</tr>
<tr>
<td>Very high</td>
<td>7.75 [3.86-15.1]</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Comparison of additional versus no additional heparin during therapeutic oral anticoagulation in patients undergoing Percutaneous Coronary Intervention

Comparison of additional versus no additional heparin during therapeutic oral anticoagulation in patients undergoing Percutaneous Coronary Intervention

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>MACCE</th>
<th>AAC +</th>
<th>AAC No (n=196)</th>
<th>AAC Yes (n=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAC = Additional anticoagulation; MACCE = major adverse cardiac and cerebrovascular events (death, MI, TVR, ST and stroke).</td>
<td>8.4%</td>
<td>3.2%</td>
<td>7.3%</td>
<td>3.2%</td>
</tr>
<tr>
<td>TTR major bleeding</td>
<td>21 (11.7%)</td>
<td>21 (11.7%)</td>
<td>21 (11.0%)</td>
<td>21 (11.0%)</td>
</tr>
<tr>
<td>Access site complications</td>
<td>10 (5.5%)</td>
<td>10 (5.5%)</td>
<td>10 (5.5%)</td>
<td>10 (5.5%)</td>
</tr>
</tbody>
</table>

Conclusion: MRS might be potentially useful information for a prediction of the incidence of CIN in the Japanese patients undergoing PCI.
Functional syntax score improves stratification of risk in patients with left main coronary artery disease

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The Functional Syntax Score (FSS) is obtained including in the computation of the Syntax Score (SS) only FFR positive lesions (i.e. FFR < 0.80). FSS has demonstrated better prognostic value as compared with SS in patients with multivessel disease (lesions of left main excluded) treated with DES implantation. The purpose of the present analysis is to assess whether FSS is better to discriminate the potential PCI-related risk in patients with left main (LM) lesions as compared with SS.

Methods and results: Patients (pts) with angiographically equivocal LM stenosis (n=209) undergoing FFR measurement were enrolled. Pts with (n=138) LM FFR < 0.80 with either deferred to optimal medical treatment or to PCI of other significantly stenotic lesions (n=75) with LM FFR < 0.80 underwent bypass surgery. SS was calculated on all angiographies. FSS was calculated by excluding from the computation LM stenosis with FFR > 0.80. Based on the SS, patients were classified in the following tertiles: 68 pts in the low (<14 SS), 69 pts in the intermediate (15-21 SS), and 72 pts in the high (<22 SS). After calculation of FSS, 67 out of 209 patients (32%) were reclassified to lower SS tertile. More specifically, out of 69 patients with intermediate SS (15-21), 37 (54%) were reclassified to lower tertile (<14). While out of 72 patients with high SS (22-42), 13 (18%) pts were reclassified to the intermediate tertile and 17 (24%) to the low tertile (<14). More specifically, out of 69 patients with intermediate SS (15-21), 37 (54%) were reclassified to lower tertile (<14). While out of 72 patients with high SS (22-42), 13 (18%) pts were reclassified to the intermediate tertile and 17 (24%) to the low tertile (<14). More specifically, out of 69 patients with intermediate SS (15-21), 37 (54%) were reclassified to lower tertile (<14). While out of 72 patients with high SS (22-42), 13 (18%) pts were reclassified to the intermediate tertile and 17 (24%) to the low tertile (<14).

Conclusion: The present study demonstrates that FSS is particularly useful in the risk stratification of patients with equivocal LM stenosis, allowing to down-grade the coronary artery disease severity in up to one third of the cases. Further studies assessing the prognostic significance of FSS in LM disease are warranted.

Impact of real time 3D-echocardiography in the assessment of right ventricular volumes and function in patients with pulmonary hypertension

I. Fabiani, L.C. Conte, C. Giannini, V. Barletta, L.A. Leo, P.S. Palla, A. Pallara, A. Balbarini, M. Mazziol, A. Di Bello, Cisanello Hospital, Department of Cardio-Thoracic and Vascular, Pisa, Italy

Background: Right ventricular (RV) function is taking last years a higher relevance as a clinical and prognostic marker in many pathophysiological conditions. The aim of the study is to point out the incremental value of real time three dimensional echocardiography (RT3DE) and Tissue Doppler imaging (TDI) in the evaluation of patients affected by pulmonary hypertension (PH).

Methods: Enrolled 42 subjects affected by PH who underwent 2D and Doppler echocardiography, RT 3D Echocardiography and TDI evaluation of RV, and an healthy control group. PH can induce itself severe functional and structural abnormalities of RV, such as RV hypertrophy, RV dilatation, RV systolic and diastolic dysfunction.

Results: RV fractional area contraction (RV FAC) and tricuspid annular plane systolic excursion (TAPSE) showed marked alterations in patients with PH compared to control group (C); RV FAC (PH: 0.30±0.08 vs C: 0.50±0.05, p<0.001; TAPSE (PH):15.4±3.1 vs C (21.0±2.5 mm, p<0.0001). 3D RV End Diastolic Volume was significantly higher in PH than in C (PH:138.5±25.1 vs. C: 83±12.6 ml, p<0.0001) as well as 3D RV End Systolic Volume (PH): 97.7±21.4 vs (C) 39.4±9.6 ml, p<0.0001. 3D RV EF was significantly lower in pulmonary hypertension group than in healthy subjects (31.6±6.8 vs C) (52.7±4.6%, p<0.0001).

Conclusions: Right systolic, systolic volume and ejection fraction evaluated by RT3DE showed a higher discriminating power in comparison respectively with 2D RV diastolic area and the relative fractional area changes in patients with pulmonary hypertension compared with controls.

RV diastolic strain rate changes with age

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Purpose: Right Ventricular (RV) diastolic functional assessment is often limited and underreported in comparison to the LV. RV diastolic function has shown changes with age similar to that of the LV. However the routine reporting of RV diastolic function is hampered by a lack of concise measurements. Strain Rate (SR), calculated via speckle tracking, is an angle and load independent measure of any other adverse event. Analysis of one-to-one propensity matched pairs showed a significantly higher risk of access site complication in patients receiving additional anticoagulation (13.1 vs. 5.7%, p=0.049).

Conclusions: Therapeutic anticoagulation treatment seems to provide sufficient anticoagulation for PCI. Additional heparins are not needed and may increase access site complications.

Impact of real time 3D-echocardiography in the assessment of right ventricular volumes and function in patients with pulmonary hypertension

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Conclusions: Right systolic, systolic volume and ejection fraction evaluated by RT3DE showed a higher discriminating power in comparison respectively with 2D RV diastolic area and the relative fractional area changes in patients with pulmonary hypertension compared with controls.
Pulmonary artery stiffness and right ventricular function in children at risk for obesity

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Purpose: Childhood obesity is associated with cardiovascular risk factors. Being at risk for overweight has been defined as having a body mass index (BMI) between the 85th and 94th percentile for age and sex. In this study, we investigate the pulmonary artery stiffness and right ventricular function in children who are at risk for overweight.

Methods: 56 children who were at risk for obesity (study group) and 40 children with a BMI between the 25th-74th percentiles (controls) were studied. The age of the studied subjects ranged from 6 to 16 years. Fasting blood levels of glucose, total cholesterol, HDL cholesterol, triglycerides, high sensitive C-reactive protein (hs-CRP) and waist circumference (WC) were assessed in both groups. Conventionally as well as right ventricular tissue Doppler was evaluated. Pulmonary artery stiffness (PAS) was evaluated utilizing the following formula (PAS=Doppler Frequency/Acceleration time).

Results: Increased PAS was observed in children who were at risk for overweight compared with the children (P=0.001). The children who were at risk for overweight have subclinical diastolic right ventricular dysfunction (P<0.05 and P<0.001 for E/A ratio and sızovolumetric relaxation time (IVRT) respectively) and higher levels of hs-CRP (P<0.01) compared to controls. RV function was significantly correlated with WC, RV wall thickness, PAS, and hs-CRP. Waist circumference and CRP (P<0.001) were the main predictors of PAS in children at risk for obesity.

Conclusions: Subclinical RV dysfunction and inflammation indices were observed in children who were at risk for overweight. The data suggest that appropriate treatment strategies for weight control are essential not only for obese children but also for those at risk for overweight.

Non-invasive assessment of right ventricular preload by Doppler echocardiography

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Several patients in critical conditions, like cardiogenic or septic shock, can have hypovolemia as a contributory factor to cardiovascular failure by decreasing cardiac preload. Assessment of fluid status, however, might be controversial in spondaneously breathing, non-ventilated patients, in which quantification data have been scarce. Although widely used, cardiac filling pressures do not reliably predict right ventricular (RV) function in these settings. In cardiac preload and ways to predict fluid responsiveness in settings outside the intensive care units to make an impact on survival in patients with shock.

Methods: 19 young healthy volunteers, aged 20-46 years (mean 31.5±0.79), were enrolled to explore the value of Doppler blood flow velocity indices of aortic outflow (LVOT), tricuspid valve (TV) and superior vena cava (SVC) inflow in predicting preload when exposed to acute simulated hypovolemia.

Results: Total cricuASP E and A inflow velocities of early and late diastolic filling and calculated E/A ratio. The peak velocities of systolic and diastolic forward SVC flow (S and D wave), atrial reversal (AR) wave and S/D ratio, the velocity-time integral of LVOT outflow Doppler spectrum and the collapse of inferior vena cava (IVC) on inspiration were all calculated.

Results: Volume decentralization resulted in a progressive decrease in TV-E velocities (58.4±50.9-39.5 c/ms, P<0.001), TV-A inflow (47.7±41.3-16.9 c/ms, P<0.03) and LVOT outflow spectrum (29.2±16.5-15.3 c/ms, P<0.001). Both systolic forward (49.0±41.7-37.0 c/ms, P<0.001) and atrial reverse flows (24.8±23.1-19.7 c/ms, P<0.003) diminished in SVC on graded LBNP. The IVC diameters could not differentiate levels of hypovolemia.

Conclusions: Our results underline the usefulness of transthoracic Doppler indices either of SVC or TV inflow and LV outflow to detect hypovolemia and to predict volume responsiveness during hypovolemic states. These easily accessible Doppler parameters may provide a simple and non-invasive means to assess directional changes in right ventricular preload, which can guide in fluid management of patients with shock at emergency departments and ‘in the frontline’ of primary care.

Impact of untreated obstructive sleep apnea on left and right ventricular myocardial function and effects of CPAP therapy

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Background: Obstructive sleep apnea (OSA) has deteriorating effect on LV function, whereas its impact on RV function is controversial. We aimed to determine the effect of OSA and continuous positive airway pressure (CPAP) treatment on left and right ventricular (LV, RV) function using transthoracic echocardiography (TTE) and 2 dimensional speckle tracking (2D ST) analysis of RV deformation capability.

Methods and results: 82 patients with OSA and need for CPAP therapy were prospectively enrolled and underwent TTE at study inclusion and after 6 months of follow up (FU). Multivariate regression analysis revealed an independent association between baseline apical RV-SI, BMI and the severity of OSA (apical RV-SI: P<0.0002, BMI: P<0.02). After CPAP therapy, LV functional parameters (LVEF: 77.7±5.1% vs 75.9±6.2%, P=0.03, stroke volume: 51.5±19.3 ml % vs 49.3±17.4 ml %, P=0.042), and apical RV-SI (P=0.001) improved significantly. The adverse effect of CPAP therapy was related to severity of OSA (LVEF: AHI 5-14: 77.7±9.4%, AHI 15-30: 59.8±7.7%, 68.6±9.3% [P<0.002], AHI >30: 54.1±12.4%, 13.6%±9.3% [P<0.001], apical RV-SI: AHI 5-14: 17.3±10.8% [P<0.05], AHI 15-30: 9.8±6.0%, 15.4±10.9% [P<0.02], AHI >30: -6.3±5.7%, -17.9±11.2% [P<0.0001]).

Conclusions: OSA seems to have deteriorating effect on LV and RV function. We found a beneficial effect of CPAP on LV and RV functional parameters predominately in patients with severe OSA, 2D speckle tracking might be of value to determine early changes in global and regional right ventricular function.

Biomarkers and imaging in early diagnosis of right ventricular dysfunction

O. Vittos1, B. Toana2, A. Vittos3, F. Halici4, E. Molveanuv5,6
1Medcenter, Bucharest, Romania; 2Clinical Emergency Central Military Hospital Dr. Carol Davila, Bucharest, Romania; 3University of Medicine and Pharmacy Carol Davila, Bucharest, Romania; 4Vater Babes National Institute, Department of Pathology, Bucharest, Romania

Background: While left ventricular dysfunction has been intensely studied, knowledge regarding the right ventricular dysfunction in diabetic patients is still incomplete.

Aims: To evaluate inflammatory biomarkers: high sensitivity C-reactive protein (hsCRP), tumor necrosis factor-alpha (TNF-alfa), lipoprotein associated phospholipase A2 (Lp-PLA2) and their correlation with right venticle strain and strain rate parameters in patients with diabetes mellitus type II.

Methods: We studied 51 patients with type 2 diabetes mellitus (DM), divided into two groups; group 1 DM with coexisting cardiovascular complications (coronary artery disease) and high blood pressure (29 patients) and group 2 DM and co-controlled high blood pressure only, with no coexisting cardiovascular complications (22 patients).

We conducted the analysis of right ventricular (RV) function through Vector Velocity Imaging and determined the inflammatory profile (hsCRP, TNF-alfa, Lp-PLA2) for each patient.

Results: In group 1, patients with type 2 diabetes and cardiovascular disease, the Lp-PLA2 activities were significantly higher, with mean value 419.46 UI, compared to group 2, being statistical significant for SbasalRV, SmidRV and SmidRV (P<0.01). We identified significant differences between groups for hsCRP and HDL cholesterol (p<0.01). A higher impairment of right ventricular longitudinal systolic function was noticed within group 1, compared with group 2, being statistical significant for SbasalRV, SimdRV and SmidRV (P<0.01). Lp-PLA2 activity was statistically positive correlated with RV strain and strain rate (p<0.01). TNF-alfa and hsCRP did not correlate with any RV echocardiographic parameters.

Conclusion: By assessing the inflammatory profile of diabetic patients, it has been revealed that, even those asymptomatic for cardiovascular diseases, have a continuous inflammatory state, together with a decrease in RV systolic function, which should be screened as well in each diabetic patient. Lp-PLA2 was the best correlated marker with RV parameters, nevertheless due to the cross-sectional design, data collected could not provide prognostic value for the investigated inflammatory markers and it is necessary to extend the study with a follow-up period.

Echo derived tricuspid dp/dt as a marker of right ventricular function

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Purpose: Right ventricular (RV) systolic function approximates prognostic significance in various disease states. RV geometry is not readily amenable to volumetric assessment by 2-dimensional echocardiography. Intraventricular pressure rate of rise (dp/dt) predicts myocardial contractility and adjusting dp/dt for the maximal regurgitant velocity (Vmax) eliminates the effect of preload. We ex-
amined the relationship of echo derived tricuspid dP/dt and dP/dt/Vmax with RV ejection fraction (EF) by cardiac magnetic resonance imaging (MRI) as a measure of RV systolic function.

Methods: Fifty cardiac MRI and echocardiograms performed within 30 days were included in the study cohort. The tricuspid regurgitation (TR) spectral doppler trace was analyzed offline. TR dP/dt calculated using simplified Bernoulli (dP/dt between 1,9 and 2,0 m/s), dP/dt/Vmax was calculated as a ratio of dP/dt and TR Vmax. RV end diastolic and end systolic volumes obtained from contouring of steady state free precession axial stack MRI images; RVEF was calculated as [(RV end diastolic volume - RV end systolic volume) / RV end diastolic volume] x 100. RV EF - 44% was considered normal.

Results: A majority (78%) of studies were adequate for measurement of dP/dt and included in the final analysis. Median age of the study population was 48 years (IQR: 36-63); 56.4% were female (n=22/39). There was moderate correlation between dP/dt and RVEF (r = 0.51, p < 0.01) which improved with dP/dt/Vmax (r = 0.59, p < 0.01). Using 400mmHg/s as the lower limit of normal for RV function, TR dP/dt had a positive predictive value of 91% and a sensitivity and specificity of 74% and 84%, respectively. Interobserver agreement and repeatability analysis of dP/dt by Plimans variance ratio test showed no significant difference (ratio of standard deviation = 0.95, 95% CI 0.90-0.99; t = -1.9, p = 0.06).

Conclusion: Tricuspid dP/dt is a reproducible measure of RV function and correlates significantly with MRI RV EF. A dP/dt of more than 400mmHg strongly predicts normal RV EF. Adjusting for preload (dP/dt/Vmax) further improves this correlation.

**P4826**

Tricuspid annular plane systolic excursion obtained in the right ventricle modified apical four-chamber view shows strong correlation with right ventricular fractional area change

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Purpose: Analysis of right ventricular (RV) function is considered to be difficult because of the complex structure. Tricuspid annular plane systolic excursion (TAPSE) is easily obtainable method for assessment of RV function. However, conventional TAPSE obtained in apical four chamber view (cTAPSE) has a disadvantage of angle dependency. The purpose of this study is to evaluate the superiority of TAPSE obtained in RV modified apical four chamber view (mTAPSE) over cTAPSE in assessment of RV function.

Methods: This study consisted of 67 patients (39 females, 55±19 years) who underwent the standard transthoracic echocardiography. Our exclusion criteria is patients with previous myocardial infarction and high plasma brain natriuretic peptide levels.

Results: Twenty patients with normal RV EF (RV ejection fraction (RV-EF) > 50%) and 47 patients with reduced RV EF (RV-EF < 50%) were included in the study cohort. The tricuspid regurgitation (TR) spectral doppler trace was analyzed offline. TR dP/dt calculated using simplified Bernoulli (dP/dt between 1.9 and 2.0 m/s), dP/dt/Vmax was calculated as a ratio of dP/dt and TR Vmax. RV end diastolic and end systolic volumes obtained from contouring of steady state free precession axial stack MRI images; RVEF was calculated as [(RV end diastolic volume - RV end systolic volume) / RV end diastolic volume] x 100. RV EF - 44% was considered normal.

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Conclusion: Tricuspid dP/dt is a reproducible measure of RV function and correlates significantly with MRI RV EF. A dP/dt of more than 400mmHg strongly predicts normal RV EF. Adjusting for preload (dP/dt/Vmax) further improves this correlation.

**P4827**

Right ventricular systolic function is highly dependent on left ventricular dysfunction in patients with previous myocardial infarction and high plasma brain natriuretic peptide levels

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Background: Although right ventricular (RV) dysfunction often coexists with left ventricular (LV) dysfunction after myocardial infarction (MI), the underlying mechanisms responsible for RV dysfunction have remained unclear in the clinical setting.

Methods: We analyzed 82 patients with previous MI with no history of RV infarction (LV ejection fraction 45±17%) and 28 age-matched normal controls (LV ejection fraction 65±5%). All patients underwent complete echocardiography including speckle-tracking strain measurements both in the LV and RV. Global RV longitudinal peak systolic strain (RV-strain) was assessed from apical 4-chamber view by using speckle-tracking strain imaging. Global left ventricular longitudinal peak strain (LV-strain) was assessed from apical 2-, 3-, and long-axis views and was calculated by averaging three strain values by using speckle-tracking strain imaging. Plasma BNP level was also assessed in all patients without (versus with) RV dysfunction.

Results: RV-strain and LV-strain were significantly reduced in patients with MI compared to normal controls (RV-strain: -18.6±25.4%, LV-strain: -12.6±17.5%, p < 0.05 vs. 0.005). Multivariable linear regression analysis indicated that only LV strain (standardized coefficients of 0.44) were independent determinants of RV-strain. When patients were divided into 3 groups according to plasma BNP levels (group A: BNP > 100 pg/ml; n = 32, group B: 100 < BNP < 500 pg/ml; n = 31, and group C: BNP < 500 pg/ml; n = 18), group C had strong correlation between RV-strain and LV-strain (r = 0.80, p < 0.05).

Conclusion: Longitudinal RV systolic function highly depends on longitudinal LV systolic function after MI especially in patients having high plasma BNP levels. These results may indicate that RV dysfunction can progress as remote remodeling which regulated in response to the increase in loading conditions after MI.
Comparison of strain measurements with speckle tracking echocardiography and velocity vector imaging in detection of RV dysfunction in patients with ischemic cardiomyopathy: a validation study with Ca

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Background: Though strain measurement has been introduced and used to measure LV function, it has been used to estimate RV function. However, variations in strain measurement by different vendors have limited the application of these techniques for assessment of RV dysfunction. We sought to compare two methods for the assessment of RV function, compared with cardiac magnetic resonance imaging (CMR).

Methods: We studied 25 patients (21 men, 66±12y) with ischemic cardiomyopathy who underwent both echocardiography and CMR. Global longitudinal strain of RV was measured with RV velocity vector imaging (GLS-VV); Siemens Medical systems) and with GLS with speckle tracking echocardiography (GLS-STE; GE Medical Systems) were measured on the same set of echo images. RV dysfunction was defined by RV ejection fraction (EF) < 50% by CMR.

Results: GLS-VVI and GLS-STE were correlated (r=0.76, P<0.001) and showed significant correlation with conventional echocardiographic parameters of RV (Table 1). GLS-VVI correlated better with RV EF (r=-0.75, P<0.001) than STE (r=-0.56, P=0.004). The best cutoff of GLS-VVI for detection of RV dysfunction was 16.9% (area under the curve = 0.89, P<0.001) with specificity and sensitivity was 97% and 55%, 93% and 61% respectively), and a value of GLS-STE was 17.2% (area under the curve = 0.70, P<0.10), sensitivity 75% and specificity 68%.

Comparison of correlations between GLS-V

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GLS-VVI</th>
<th>GLS-STE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation Coefficient (r)</td>
<td>P-value</td>
<td>Correlation Coefficient (r)</td>
</tr>
<tr>
<td>CMR RVF</td>
<td>-0.748</td>
<td>-0.001</td>
</tr>
<tr>
<td>RVFAC</td>
<td>-0.701</td>
<td>-0.001</td>
</tr>
<tr>
<td>TAPSE</td>
<td>-0.675</td>
<td>-0.001</td>
</tr>
<tr>
<td>RV TDI index</td>
<td>0.605</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Conclusion: Although GLS-VVI and GLS-STE show significant correlations with CMR RVF and other conventional echocardiographic parameters of RV function, GLS-VVI appears superior to GLS-STE in the detection of RV dysfunction.

Right ventricular regional systolic function and dyssynchrony in patients with pulmonary hypertension evaluated by three-dimensional echocardiography

D.H. Kong, X.H. Shu, C.Z. Pan, L.L. Cheng, D.X. Zhou, J.B. Ge. Zhongshan Hospital of Fudan University, Shanghai, China, People’s Republic of China

Objective: Right ventricular (RV) function is of diagnostic and prognostic importance in patients with pulmonary hypertension (PH). The purpose of the present study was to evaluate RV regional systolic function and dyssynchrony in patients with PH using real-time three-dimensional echocardiography (RT3DE).

Methods: A total of 70 patients with PH and 26 age-matched controls were enrolled. RT3DE images were acquired and analyzed to obtain RV regional (in-flow, body, out-flow) ejection fraction (EF) and to minimum systolic volume (Tmsv). The dyssynchrony index was calculated as the standard deviation of Tmsv in three RV segments corrected by heart rate (Tmsv-SD%). Conventional echocardiographic parameters including RV fractional area change (FAC), tricuspid annular peak systolic velocity (S), RV myocardial performance index (MPI) as well as echocardiography-estimated pulmonary artery systolic pressure (PASP) and pulmonary vascular resistance (PVR) were recorded. The patients with PH were divided into 3 groups as mild PH (PASP: 40mmHg–49mmHg), moderate PH (PASP: 50mmHg–69mmHg) and severe PH (PASP:≥70mmHg). Results: Average RT3DE acquisition and analyze time was less than 10 minutes. RT3DE image quality was adequate to analyze in more than 95% of all subjects. RV global and regional EF measured by RT3DE correlated with FAC, S and MPI in all patients. Aortic valve area (AVA) was different: type I were thin and rarely calcified; type II have intermediate characteristics (Table). All AAP ulcerations were different: type I are thin and rarely calcified; type III are thicker and often calcified; type IV wood was 40.5% for EF-inflow and EF-global was lower in all patients with PH (P<0.05), while EF-body was decreased in moderate and severe PH (P<0.05) and EF-outflow changed in severe PH (P<0.001). RV-SD% in type II moderate PH was similar to that in the control group and was significantly lowered in severe PH (P<0.05). EF-inflow and EF-global was lower in all patients with PH (P<0.05), while EF-body was decreased in moderate and severe PH (P<0.05) and EF-outflow changed in severe PH (P<0.001). The relationship between other systolic parameters with PASP or PVR was weaker or not significant. The optimal cut-off value in determining PASP≥70 mmHg and PASP>70 mmHg was 40.5% for EF-inflow (sensitivity and specificity was 97% and 55%, 93% and 61% respectively), and 42.2% for EF-global (sensitivity and specificity was 97% and 76%, 90% and 85% respectively).

Conclusions: In patients with PH, RV inflow and global systolic function was impaired in inverse relationship with PASP and PVR. RV systolic synchronicity was impaired in severe PH. Evaluation of RV regional systolic function using RT3DE method may play a potential role in the non-invasive assessment of the severity of PH.

AORTA AND AORTIC VALVE

N. Hammoudi1, M. Haddaden2, L. Boubrì3, C. Meuleman4, S. Ederuy5, P.L. Michel6, S. Alamowitch7, A. Cohen8, 1AP-HP - Hospital Pitié-Salpêtrière, Department of Cardiology, Paris, France; 2AP-HP - University Hospital Ambroise Pare, Department of Cardiology, Boulogne-Billancourt, France; 3AP-HP - Hospital Pitié-Salpêtrière, University Pierre & Marie Curie Paris VI, Dept of Cardiology, Paris, France; 4AP-HP - Hospital Saint Antoine, Paris, France; 5AP-HP - Hospital Tenon, University Pierre & Marie Curie Paris VI, Dept of Neurology, Paris, France; 6AP-HP - Hospital Tenon, University Pierre & Marie Curie Paris VI, Dept of Cardiology, Paris, France

Transesophageal echocardiography (TEE) is the reference method for characterization of aortic atherosclerotic plaques (AAP) at risk of stroke. To evaluate the feasibility and contribution of 3D TEE in the evaluation of AAP, we prospectively included 82 patients referred for TEE. In addition to 2D, a 3D study of AAP of the descending and horizontal thoracic aorta was performed. 308 AAP were identified in 2D, 98% of them were analyzed using 3D. We identified 3 morphological 3D types of AAP (flakes, plaque, 3D characteristics of the 3D types were different: type I are thin and rarely calcified, type II are thicker and often calcified; type II have intermediate characteristics (Table). All AAP ulcerations seen in 2D were identified in 3D. Thickness measurements from 3D correlated well with measurements performed on the 2D acquisitions (r=0.91; p<0.001). Area measurements of AAP were feasible in 58%, 14% and 23% of 3D types I, II and III, respectively. The areas of type I AAP were not correlated with those of thickness in 2D.
Assessment of the valvuloarterial impedance during transthoracic echocardiography to study the gender difference in regression of myocardial hypertrophy after aortic valve replacement

3D types of plaques: 2D characteristics

<table>
<thead>
<tr>
<th>Type</th>
<th>I (n=115)</th>
<th>II (n=97)</th>
<th>III (n=89)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descending Aorta (mm)</td>
<td>77</td>
<td>69</td>
<td>49</td>
<td>189</td>
</tr>
<tr>
<td>Horizontal Aorta (mm)</td>
<td>39</td>
<td>34</td>
<td>40</td>
<td>112</td>
</tr>
<tr>
<td>Plaque thickness (mean ± SD, mm)</td>
<td>1.2±0.5</td>
<td>2.6±1.2</td>
<td>3.2±1.5</td>
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<tr>
<td>Net calcified plaques (%)</td>
<td>103 (80.5)</td>
<td>22 (17.2)</td>
<td>9 (2.4)</td>
<td>128</td>
</tr>
<tr>
<td>Vary calcified plaques (n,%)</td>
<td>3 (4.2)</td>
<td>13 (18.3)</td>
<td>55 (77.5)</td>
<td>71</td>
</tr>
</tbody>
</table>

Methods: 80 patients with a severe aortic valvular disease (stenosis or regurgitation) were evaluated with a transthoracic echocardiography and MSCT to measure the thoracic aorta at different levels: sinuses of Valsalva, sinotubular junction and ascending aorta. Three different echocardiographic methods were used: leading edge to leading edge, inner to inner and outer to outer and then compared to the ones obtained from MSCT. The interobserver and intraobserver variability was also performed.

Results: Transthoracic echocardiographic diameters were obtained in all patients but 3 (4%) because of poor acoustic window. The three methods showed an excellent interobserver and intraobserver variability, however, the inner to inner method presented the best reproducibility. Also, the inner to inner method showed the best correlation with MSCT for the assessment of thoracic aorta diameters (intraclass correlation coefficient): sinuses of Valsalva 0.83, sinotubular junction 0.87, and ascending aorta 0.88. Mean difference between TTE and MSCT in measuring the ascending aorta were: by inner to inner 0.25±0.6 mm, leading to leading -0.7±0.43, and outer to outer -3.2±1.23.

Conclusions: Transthoracic echocardiography is an accurate technique for the assessment and follow-up of thoracic aortic diameters in valvular patients. The inner to inner approach is the method that shows the best agreement with MSCT measurements of aortic root dimensions.

Assessment of the valvuloarterial impedance calculated with the use of 3-dimensional transesophageal echocardiography

Methods: We analyzed 74 patients (8±10 years) with moderate to severe AS. Ellipticity of the left ventricular outflow tract (LVOT) and the sinotubular junction (STJ) were calculated as the short axis dimension divided by the long axis one. The areas of LVOT and STJ were evaluated using circular formula (πr²) by 2-dimensional transthoracic echocardiography (2D-TTE) and using direct measurement by 3-dimensional transesophageal echocardiography (3D-TEE). Zva was calculated as the estimated left ventricular systolic pressure (systolic arterial pressure + net mean pressure gradient taken into account post-stenotic pressure recovery) divided by the stroke volume index.

Results: Systolic blood pressure was 123±17 mmHg; peak EF 56±5% and; mean pressure gradient, 41±14 mmHg. The ellipticity of LVOT and STJ was 0.77±0.10 and 0.59±0.05, LVOT and STJ areas using 2D-TTE (3.6±1.1, 5.0±1.4 cm², respectively) was smaller than those using 3D-TEE (4.4±1.0, 5.4±1.3, respectively, p < 0.01); subsequently, energy loss index using 2D-TTE was smaller than that using 3D-TEE; consequently, Zva using 2D-TTE (4.2 mm Hg/ml/m², 3.4-2.6-4.2, p < 0.01).

Conclusions: Two D-TTE overestimated the value of ELI relative to 3D-TEE due to the elliptical shape of the aortic root. It is desirable to use 3D TEE in the evaluation of Zva for risk stratification in patients with AS.

Incremental accuracy of transesophageal echocardiography over transthoracic approach for description of functional anatomy of aortic regurgitation

Background: Preoperative description of mechanisms of Aortic Regurgitation (AR) is essential for planning valve sparing surgery (VSS). Either transesophageal (TEE) or transthoracic echocardiography (TTE) provide detailed anatomic view of aortic valve and ascending Aorta (AA) and information about dimensions and dynamic function of its components. Objective. To establish diagnostic value of multiple TEE in comparison with TTE for definition of functional anatomy of AR.

Methods: Using surgical observations as a reference, overall accuracy of TEE and TTE were calculated for both functional and anatomic classification of AoR in 51 patients operated for AR. Incremental accuracy of TEE over TTE was calculated as the ratio of the difference between their accurate diagnoses to the total number of cases examined and tested using McNemar’s test.

Results: Overall accuracy of TEE for functional classification was high (82%), but accuracy of TEE was higher (86%). Percentage of errors of TEE corrected by TEE was – 50% for all specific lesions of aortic valve and AA. Incremental accuracy of TEE was low (≤ 10%) except for diagnosis of aortic valve prolapse (AVP) associated with AA dilatation (16%) and for classification of AR mechanisms (20.5%). Agreement between both modalities in AR jet direction was good (kappa = 0.85) eccentric jet in 12/15 cases of AVP in TEE (p<0.0001) and in 11/15 in TTE (p=0.002).

Conclusions: Both TEE and TTE provide high degree of accuracy. Incremental value of TEE for AVP and mechanisms was notable. In the setting of VSS, failure to identify pre-existing AVP may be responsible for unsuccessful operation. Therefore, preoperative TEE may help the surgeon to distinguish valves with geometric distortion amenable to repair from those that require replacement.
and 6 months after operation in 47 patients, 28 women and 19 men, undergoing aortic valve replacement for isolated aortic stenosis.

Results: Preoperatively, women and men had similar ejection fraction (56 and 59%) and left ventricular mass (142 and 148 g/m²). Postoperatively, there was no difference in effective valvular orifice area index, mean transvalvular pressure gradient between men and women. Two weeks after operation, increased LV mass persisted in men (131 g/m²) although LV hypertrophy in women (119 g/m²) regressed to the similar level of 6 months (121 g/m²). LV mass in men was similar to those in women in 6 months after operation.

Figure 1

Conclusion: Women adapt to pressure overload quickly than men, while men caught up to women in 6 months after operation.

P4837 Age-related increase in aortic stiffness affects longitudinal myocardiocadial function and ventricular-arterial coupling in both systolic and diastolic phase in normal subjects

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Background: An increased arterial stiffness is an established mechanism contributing to LV dysfunction in hypertension and in age-related atherosclerosis. It is less clear whether an age-related increase in large artery stiffness affects LV performance even in young-to-middle-aged healthy subjects.

The aim of this study was to evaluate the possible associations of aortic stiffness with LV longitudinal myocardiocadial function and ventricular-arterial (V-A) coupling in normal subjects.

Methods: A cohort of 134 subjects without clinical CV disease and atherosclerotic risk factors (69 males; mean age 39±13 years, range 18-61, LV EF ≥ 55%) was studied. Aortic stiffness was estimated by carotid-femoral pulse wave velocity (PWV) measured by Compilor (Alam, Vincennes, France).

An ultrasound system (Alpha 10, Aloka, Tokyo, Japan) was used to measure LV mass (LVM) and LV longitudinal myocardiocadial velocities (Sv, Ev, Av) by tissue veloc- imaging (TVI) of the mitral annulus. The same US system was applied to esti-mate V-A coupling by means of a net wave intensity analysis (Wl) algorithm implemen-ted on carotid US. From simultaneous recordings of carotid diameter-derived pressure waveform and flow velocity signals, Wl is obtained as the product of the pressure and flow derivatives throughout the cardiac cycle. A first positive peak (W1) in early systole is related to dp/dt of contraction, and a second peak (W2), late systolic, is related to LV early diastolic suction and aortic compliance.

Results: Mean PWV was 7.8±1.7 m/s, PWV was directly related (p<0.0001) with age (r=0.71), systolic BP (r=0.47), LVM (r=0.37) and Av (r=0.38), and inversely with Sv (r=-0.29, p<0.0001). W1 (r=0.48, p<0.0001) and W2 (r=0.27, p<0.0001). No relations were found between PWV and stroke vol- ume, cardiac output and ejection fraction. In multiple regression model entering PWV as dependent variable and all co-variates in univariate analyses as independent variables, age resulted as a main determinant of PWV, explaining as much as 52% of its variance. PWV, when entered in multiple regression mod- els with tissue myocardial velocities and indices of V-A coupling as dependent variables, resulted as the only independent determinant of these measures.

Conclusions: In a cohort of healthy young-to-middle-aged subjects without CV disease risk factors, an age-related increase in aortic stiffness is associated with a relative reduction in longitudinal myocardiocadial function, systolic and early diastolic, as well as in LV contractile function and early diastolic suction, while global pump function seems to be unaffected.

P4840 A novel visualization of aortic arch stiffness using pulse wave tissue Doppler imaging: correlation with complicated aortic plaque

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Purpose: Elevated aortic stiffness parameter β (Adi), defined as β = (systolic blood pressure-diastolic blood pressure)/(Dmax/Dmin), is a simple and powerful logarithm, Dma is maximum aortic lumen diameter, and Dmin is minimum aortic lumen diameter by transeophageal echocardiography (TEE), and presence of complicated aortic arch plaque (CAP) provide prognostic information about cerebrovascular disease risk. However, this requires offline calculation and measurement of blood pressure during performance of TEE. Recently, ultrasound pulse wave tissue Doppler imaging (PW-TDI) offers a new technique for assessing aor- tic wall pathology. The purpose of this study was to investigate whether this tech- nique provides a new marker of aortic arch stiffness and correlates with CAP and atherosclerotic parameters.

Methods: We measured wall motion velocities in the aortic arch using PW-TDI in 198 consecutive cases that had undergone TEE with a 2.0mm sample volume placed at the lateral wall of the aortic arch. PW-TDI values for peak systolic epi- cardiac velocity (Vs) and peak systolic acceleration (Vdd) were obtained from both a short axis view and a long axis view of the aortic arch. CAP was defined as presence of atheroscle- rotic plaque ≥4mm or ulcerated plaque in aortic arch as assessed by TEE. We classified patients into two groups: those with CAP (n=80, 70.3±11.7 years) and those...
without CAP (n=118, 63±13years). Vs and Vd were compared between groups and with conventional vessel parameters including cardio-ankle vascular index (CAVI, calculated from blood pressure and pulse wave velocity), ankle brachial pressure index (ABI), and carotid plaque score (PS, a composite index based on carotid artery plaque thicknesses).

**Results:** Comparing patients with vs. without CAP, Vs and ABI were significantly decreased (2.9±1.2 vs. 3.8±1.3 cm/sec, p<0.001; 1.6±0.5 vs. 2.0±0.8 cm/sec, p<0.001, 0.88±0.23 vs. 1.10±0.12, p<0.001, respectively), and AoP and PS were significantly increased (17.4±12.5 vs. 12.3±8.6, p<0.01; 9.0±5.0 vs. 5.3±4.8, p<0.001, respectively). Furthermore, Vs and Vd were significantly correlated with AoP (r=0.381, p<0.001 and r=0.348, p<0.001, respectively), CAVI (r=-0.328, p<0.0001; respectively), and with conventional vessel parameters including cardio-ankle vascular index (CAVI), calcification index (CIMT), and carotid plaque score (PS, a composite index based on carotid artery plaque thicknesses).

**Conclusions:** Evaluation of Vs and Vd using PW-TDI in the aortic arch wall may be a novel and easily acquired indicator of aortic arch stiffness, and also correlates with several conventional vessel parameters.

**P4841**

**High-resolution vascular ultrasound imaging for accurate measurement of carotid intima-media thickness**

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**Purpose:** Several clinical trials have used carotid intima-media thickness (CIMT) measured using the ultrasound B-mode image to monitor the progression of cardiovascular diseases. However, its accuracy and reliability is not enough to predict cardiovascular risk. In this study, we employ an non-invasive high-range-resolution ultrasound imaging method to improve the accuracy in ultrasound measurement of CIMT.

**Methods:** The imaging method used in this study is based on frequency domain interferometry (FDI), where optical coherence tomography also uses this technique in optics to acquire high quality images of the human retina. We applied the FDI imaging method to both the simulation and experimental data. The experimental data were acquired by a commercial ultrasonographic device with a 7.5 MHz linear array probe. In vitro and in vivo experiments, we used a swine femoral artery and a living human carotid artery, respectively.

**Results:** The simulation study shows that CIMT value estimated using the conventional technique varies with the echo intensity returned from lumen-intima interface and from media-adventitia interface; in contrast, the FDI imaging method succeeded to measure CIMT accurately. The FDI imaging method also depicted high-range-resolution images of a living human carotid artery in vivo and a fresh swine femoral artery in vitro, as shown in the figure. The in vivo results indicates that the FDI imaging method has the potential to estimate CIMT with an estimation error of less than 0.01 mm.

**Conclusions:** The simulation and in vitro results indicate that the FDI imaging method largely improves the accuracy in ultrasound measurement of CIMT. We believe that the FDI imaging method helps the appearance of a reliable indicator that predicts cardiovascular risk.

**P4843**

**The relation between the CHADS2, CHA2DS2-VASc score and echocardiographic parameters of thromboembolism in patients with atrial fibrillation**

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**Background:** CHADS2 score has been revised as CHA2DS2-VASc score for better embolic risk stratification in patients with AF. The aim of this study was to evaluate the relation between 2 clinical risk scores and echocardiographic parameters of embolism in AF patients.

**Methods:** 365 (M=305, mean age=55±10.4) patients with non-valvular AF who had trans-thoracic echocardiography and trans-esophageal echocardiography were enrolled. CHADS2 and CHA2DS2-VASc scores were calculated and correlated to echocardiographic findings. LA volume, LA emptying fraction (EF), LAA emptying fraction (EF), LAA EF, the presence of dense SEC in left atrium, LA heart rate, and tricuspid hypertrophy (LH) (defined as >115 mm2/g in men, >95 mm2/g in women) were evaluated.

**Results:** Increased LAV(LAVI) was found in 143 patients, impaired LAEF(<30%) in 130 patients, decreased LAA emptying velocity(>20cm/s) in 46 patients, decreased LAA EF(<30%) in 136 patients, SEC in 10 patients and LA thrombus in 2 patients. The patients with higher than 2 CHADS2 and CHA2DS2-VASc was 65 and 182 respectively. Higher than 2 CHADS2 and CHA2DS2-VASc score was related with increased LAV, low LAEF, the presence of LVH. But low LAA EF and low LAA emptying velocity was related with higher than 2 CHADS2-vasc score only. The presence of SEC was related with higher CHA2DS2-VASc score. But the presence dense SEC and thrombus was associated with higher than 2 CHA2DS2-VASc score only (Table 1).

**Conclusions:** Higher CHADS2 and CHA2DS2-VASc scores were correlated with echocardiographic markers of LA dysfunction. But LAA dysfunction was associated with higher than 2 CHADS2-vasc score only. CHA2DS2-vasc score appears to be more sensitive than CHADS2 score in detecting high risk patients.
Assessment of left atrial deformation and dysynchrony by three-dimensional speckle tracking imaging: comparative studies in healthy subjects and patients with atrial fibrillation

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Purpose: Real-time full-volume 3D echocardiography (3DE) allows rapid and non-invasive measurement of left (LA) and right atrial (RA) volume. Different algorithms from different commercial providers are available. Older software requires manual tracing of endocardial contours. Recently software with semiautomatic endocardial contour finding algorithms has become available, which considerably speeds up the procedure. Our aim was to compare, in the same data set, LA and RA volume determined by an algorithm involving manual tracing to values obtained by a software algorithm with semiautomatic contour detection.

Methods: 88 patients were studied by real-time 3DE. Atrial volume was measured using a multiplane interpolation method algorithm (CardioView v1.3, Tomtec) with manual planimetry of 8 equidistant slices. These volumes were compared with atrial volume determined by the QLAB 7.1 software (Philips) using a semiautomated border detection method.

Results: Linear regression showed for both LA and RA an excellent correlation between volumes determined by Tomtec and QLAB software (r2 = 0.95 and 0.89 respectively, p < 0.001). Bland-Altman analysis of Tomtec versus QLAB volume determination showed rather narrow 95% limits of agreement (-12 to +16 cc for LA volume and -12 to +14 cc for RA volume) with a minimal slight bias of +1.9 ± 7 cc and +0.8 ± 6.5 cc respectively by the Tomtec method.

Conclusion: The QLAB 7.1 semiautomated border detection method shows excellent agreement with volumes determined by Tomtec software and allows the older more time consuming multiplane interpolation method by the Tomtec software, with only slight underestimation. The results indicate that values of left and right atrial volume obtained by either algorithm can be compared, for example during follow-up examinations.
Atrial fibrillation and atrial function

Table 1

<table>
<thead>
<tr>
<th>Reservoir function</th>
<th>Controls (n=27)</th>
<th>Mild MR (n=47)</th>
<th>Moderate/severe MR (n=25)</th>
<th>Overall</th>
<th>P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA total emptying</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fraction</td>
<td>42.6±9.4</td>
<td>41.3±7.5</td>
<td>34.7±10.1</td>
<td>0.005</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>S-LA (cm²)</td>
<td>20.3±5.6</td>
<td>19.8±4.3</td>
<td>15.3±3.6</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
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<tr>
<td>Conduit function</td>
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<tr>
<td>LA passive emptying</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fraction</td>
<td>22.9±8.8</td>
<td>20.8±8.6</td>
<td>20.6±8.9</td>
<td>0.42</td>
<td>0.63</td>
<td>0.39</td>
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<tr>
<td>S-LA (cm²)</td>
<td>15.5±5.4</td>
<td>9.8±4.0</td>
<td>8.7±4.1</td>
<td>0.48</td>
<td>0.33</td>
<td>0.06</td>
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<td>Booster pump function</td>
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<tr>
<td>LA active emptying</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fraction</td>
<td>25.7±7.3</td>
<td>25.7±7.3</td>
<td>17.6±10.1</td>
<td>0.0005</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>S-LA (cm²)</td>
<td>9.7±3.5</td>
<td>10.1±3.3</td>
<td>6.1±4.2</td>
<td>0.0001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

P-value 1, controls vs. moderate/severe MR; P-value 2, mild MR vs. moderate/severe MR.

References

1. University Hospital of Heidelberg, Heidelberg, Germany; 2. Second University of Naples, Naples, Italy; 3. Clinic Grosshansdorf, Grosshansdorf, Germany; 4. University of Salerno, Salerno, Italy

Background: Right atrial (RA) size is important in several indications as for screening, diagnosis and follow-up assessment in patients with pulmonary hypertension. The objective of this paper was to define normal cut-off values for RA area by echocardiography in healthy subjects.

Methods: In this prospective study 880 healthy adult subjects (mean age 28±5.9 years, 38% female, 385 top-level endurance athletes, 255 strength athletes and 230 non-athletes) were examined by echocardiography. For comparison we performed a meta-analysis of 9 previously published studies (1979-2010) describing RA area in healthy subjects (n=924). Statistical analysis included the calculation of 95% quantiles for defining cut-off values and the identification of possible confounding factors.

Results: Mean RA area was significantly larger in endurance athletes as in non-athletes (15.4±2.0 cm² vs 12.8±1.6 cm² and 12.3±2.0 cm², p<0.001). RA area correlated significantly with age, gender, body surface area and endurance exercise training and was similar in previously described 624 healthy adults (12.6±3.8 cm²). 95% quantiles for RA area of all investigated non-endurance trained subjects was 15.2 cm² (95% confidence interval 14.7-15.7 cm²) in females and 16.2 cm² (95% confidence interval 15.8-16.6 cm²) in males.

Conclusion: To our knowledge, this is the largest data set to describe RA size in adult healthy subjects (aged below 50 years). Cut-off values for RA area were significantly different in females (15 cm²) and males (16 cm²). This is clinically relevant. Age, gender, body surface area and high level endurance exercise training were confounding factors of RA area. Further investigations in subjects aged >50 years should be performed.

P4849

Reduced atrial reservoir function in fabry disease using Doppler strain imaging

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Purpose: Fabry disease is associated with progressive concentric left ventricular hypertrophy (LVH), with subsequent diastolic dysfunction and left atrial enlargement. Atrial strain rate measures myocardial deformation and may be used to quantify phasic atrial function. The aim of this study was to evaluate the impact of Fabry disease, if any, on left atrial function using Doppler derived strain rate imaging.

Methods: Transthoracic echocardiograms were performed on 24 Fabry patients; without LVH (n=10) and with LVH (n=14), and were compared to age and gender matched Normals. Doppler derived atrial strain (SI) and strain rate (SIR) were measured from 4 segments in the apical 4 and 2 chamber views of the left atrium and mean global strain and strain rate calculated. Systolic and diastolic SI, systolic S-derivative (S-derivative function), early diastolic E-derivative (conduit function) and late diastolic A-derivative (contractile function) were measured.

Results: LV mass and left atrial volume were significantly higher in the Fabry group with LVH. Fabry patients had significantly reduced S-der rates, independent of LVH, compared to normals. E-der was selectively reduced only in Fabry patients with LVH. There was no significant difference in systolic SI, diastolic SI and A-der among the groups.

Conclusions: Fabry disease is associated with reduced atrial compliance and reservoir function, irrespective of the presence of LVH, suggesting a coexistent atrial myopathy. The reduction in E-der with LVH reflects the associated reduction in left atrial conduit function. These results suggest that Fabry cardiomyopathy involves not only the ventricle but also the atrium. Consequently, measurements of left atrial reservoir function and compliance may be useful in subclinical diagnosis of Fabry disease.

P4850

Evaluation of left atrial appendage dysfunction by strain imaging using transthoracic echocardiography


Background: Left atrial appendage (LAA) thrombus is common cause of cardioembolic stroke. LAA dysfunction, which can induce thrombus formation, is usually evaluated by LAA peak flow velocity measured by transesophageal echocardiography (TEE), but it is a semi-invasive procedure. Therefore we investigated whether LAA dysfunction can be evaluated by recently developed speckle tracking strain imaging using noninvasive transthoracic echocardiography (TTE).

Methods: Consecutive 55 patients, who underwent TEE to rule out thrombus or evaluate valvular disease, were enrolled. Immediately before TEE, we observed LAA by parasternal short-axis view using TTE. A following TTE parameter was evaluated as LAA dysfunction in this study: LAA shortening fraction which was defined as the difference between maximum and minimum longitudinal strain of LAA. We compared LAA shortening fraction with classical TEE parameter, LAA peak flow velocity and also analyzed the parameter in sinus or atrial fibrillation group separately.

Results: LAA shortening fraction was significantly correlated with LAA peak flow velocity measured by TEE (r=0.641, P<0.001). In addition, LAA shortening fraction was significantly higher in sinus rhythm group (35.6±15.3% vs 25.3±15.7%, P=0.002). LAA thrombi were found in three patients, whose rhythm were all atrial fibrillation and they were all on adequate anti-coagulant therapy. LAA shortening fraction of these three patients showed significantly worse value than the other patients in atrial fibrillation group (10.5±3.92% vs 26.7±15.7%, P<0.001).

Conclusion: LAA dysfunction including possible thrombus formation can be evaluated noninvasively by strain imaging using transthoracic echocardiography.

P4851

Comparison between two-dimensional and real-time three-dimensional speckle tracking echocardiography in the assessment of left atrial structure and function

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Purpose: Two-dimensional speckle tracking echocardiography (2-DSTE) using Simpson’s method has been recently used to assess left atrial (LA) volume (LAV) and function. To evaluate the accuracy of 2-DSTE, we compared 2-DSTE with 3-DSTE as a reference standard because major advantage of 3-DSTE is the improvement of accuracy in the evaluation of cardiac chamber volume without any geometrical assumption.

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Methods: We measured phasic LAV (max., min. and pre-atrial contraction (AC) volume) and emptying function (EF) (total, passive and active EF) and LA peak strain by 3-DSTE (Atriala) which can provide time-LA volume curve with volume rates (2D-4Vps) and by 2-DST from apical 2, 3 and 4-chamber views in 61 sub-
jects. Parameters were compared between 2-DSTE and 3-DSTE.

Results: LAV and function were easily and rapidly obtained by 3-DSTE. There was a good correlation between LAV by 3-DSTE and LAV in 2, 3, 4-chamber views and the average of these three views by 2-DSTE (r=0.76, 0.80, 0.76 and 0.84, p<0.001, respectively). LA total and passive EF in 4-chamber view by 2-
DSTE was decreased compared to 3-DSTE despite no difference in LA peak strain. Phasic LAV in 3-chamber view by 2-DSTE was decreased and LA phasic function was increased compared to 3-DSTE (table).

Table 1. LA function and structure assessed by 3-D and 2-D speckle tracking

<table>
<thead>
<tr>
<th>3-DSTE</th>
<th>2-DSTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max. LAV, ml</td>
<td>52.2±13.4</td>
</tr>
<tr>
<td>Min. LAV, ml</td>
<td>29.0±9.4</td>
</tr>
<tr>
<td>PVE AC LAV, ml</td>
<td>41.6±12.2</td>
</tr>
<tr>
<td>Total EF, %</td>
<td>46.5±9.1</td>
</tr>
<tr>
<td>Passive EF, %</td>
<td>30.8±5.1</td>
</tr>
<tr>
<td>Active EF, %</td>
<td>23.2±10.2</td>
</tr>
<tr>
<td>LA strain</td>
<td>19.7±5.7</td>
</tr>
<tr>
<td>LA global strain</td>
<td>17.6±7.5</td>
</tr>
<tr>
<td>*p&lt;0.05 vs. 3-DSTE.</td>
<td></td>
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</tbody>
</table>

Conclusion: Although LA volume and function assessed in 3 and 4-chamber view by 2-DSTE and 3-DSTE were comparable to each other, LA function was improved in 3-DSTE compared with 2-DSTE. LA strutcture was an under-estimated compared to 3-DSTE, which showed more reliable data for the LA. This study demonstrated 3-DSTE will be more promising method in assessment of LA structure and function than 2-DSTE.

Methods: Prolonged atrial electromechanical conduction in Left atrium deformation and cardiac dysfunction. Particularly, hypertrophic cardiomyopathy (HCM) and cardiac amyloidosis are representative disorders of left ventricular hypertrophy to progress LA remodeling. Recently, atrial electromechanical conduction time (EMT) measured by tissue Doppler method was reported as the useful parameter of recurrence of atrial fibrillation after cardioversion. However, this method has limitations having angle dependency and tethering effects by adjacent cardiac Anatomy.

Methods: This study was aimed to clarify the impact of EMT measured by speckle tracking echocardiography on LA remodeling and outcomes in 38 patients with HCM (mean 59 years) and 10 patients with biopsy-proved cardiac amyloido-

Purpose: Device occlusion of the left atrial appendage (LAA) in patients at high risk of thromboembolic stroke but unable to be anticoagulated has emerged as an established therapeutic option. 2D transesophageal echocardiography (TOE) is currently used to determine the appropriate size of an LAA occluder device. The LAA anatomy is highly variable and the orifice is oval shaped and 3D echocardiography may underestimate the LAA ostium even if a range of measurements are taken. This study examined the impact of left atrial appendage size on device occlusion.

Results: All LAA orifices were oval in shape. The mean LAA orifice diameter on 2D TOE imaging was significantly smaller at 17.9±4.9 mm (range 10.6 to 22.1 mm) compared to the mean LAA orifice diameter on 3D TOE imaging which was 22.8±5.4 mm (range 17.9 to 27.7 mm). The working LAA depth was similar using both methods: 2D 18.3mm (5.0mm,7.8–36.0mm), MPR 18.8mm (6.3mm, 7.8–38.0mm).

Conclusion: Accurate LAA orifice measurement is important for successful implantation and complete occlusion of the LAA. The LAA orifice is oval in shape and 2D TOE may significantly underestimate the diameter of the LAA orifice by approximately 1.0mm. 3D TOE and image analysis are recommended for accurate and reliable measurement of the LAA orifice. Such improved measurement techniques facilitate accurate device selection during LAA occlusion.

Methods: Prospective, longitudinal study of 62 consecutive patients referred to CRT between October 2009 and March 2010. Patients with atrial fibrillation were excluded (n=14). Clinical, demographic and analytical data were collected at the time of implantation. Standard echocardiography evaluation and comparison tracking LA longitudinal strain analysis were performed prior and 6 months after CRT. Regarding strain analysis, a global LA peak systolic longitudinal value was collected and roof LA values. A responder was defined by a 15% reduction in left ventricular end systolic volume.

Results: Mean age of the population was 65±10 years. 67% were male and there was an idiopathic etiology predominance (75%). The majority of the population was in NYHA class III (81%). The mean basal QRS duration was 143±21 ms and the mean left ventricle ejection fraction was 24±7%. Forty nine percent of patients were considered responders. There was a significant improvement in LA global peak systolic longitudinal strain (12.0±5.2 vs 14.1±5.9, p<0.01) with CRT. A similar improvement was identified in septal (12.4±7.4 vs 15.5±6.8, p<0.01), lateral (12.7±6.1 vs 14.4±5.8, p<0.01) and roof LA (10.0±5.2 vs 13.4±5.9, p<0.01) longitudinal strain. There was a significant negative correlation between LA peak systolic longitudinal strain and LA volume (r=-0.36, p=0.02). Basal LA global strain was not a predictor of CRT response (12.8±5.2 vs 11.3±5.1, p=0.33). There were no significant correlation between LA longitudinal strain and left ventricular Yu index.

Conclusions: In our population LA longitudinal strain improved significantly with CRT.

Methods: Late atrial electromechanical conduction in hypertrophic cardiomyopathy and cardiac amyloidosis.

Conclusion: Although LA volume and function assessed in 3 and 4-chamber view by 2DSTE and 3-DSTE were comparable to each other, LA function was improved in 3-DSTE compared with 2-DSTE. LA structure was an under-estimated compared to 3-DSTE, which showed more reliable data for the LA. This study demonstrated 3-DSTE will be more promising method in assessment of LA structure and function than 2-DSTE.

Methods: Prolonged atrial electromechanical conduction in hypertrophic cardiomyopathy and cardiac amyloidosis.

Conclusion: Although LA volume and function assessed in 3 and 4-chamber view by 2DSTE and 3-DSTE were comparable to each other, LA function was improved in 3-DSTE compared with 2-DSTE. LA structure was an under-estimated compared to 3-DSTE, which showed more reliable data for the LA. This study demonstrated 3-DSTE will be more promising method in assessment of LA structure and function than 2-DSTE.

Methods: Prolonged atrial electromechanical conduction in hypertrophic cardiomyopathy and cardiac amyloidosis.

Conclusion: Although LA volume and function assessed in 3 and 4-chamber view by 2DSTE and 3-DSTE were comparable to each other, LA function was improved in 3-DSTE compared with 2-DSTE. LA structure was an under-estimated compared to 3-DSTE, which showed more reliable data for the LA. This study demonstrated 3-DSTE will be more promising method in assessment of LA structure and function than 2-DSTE.
Supranormal diastolic function in elite endurance-athletes is related to left atrial geometry and function

Athletes 51.4 ± 15 years, 44 male were enrolled: 40 endurance athletes and control group of 24 age- and sex-matched sedentary subjects. LA geometry was assessed by volumes at the MVO (MVOV), MVC (MVCV), and at the beginning of the P wave (PV), while LA function by passive EF (E) as PV-MVCV/PV. LA deformation was measure by STI: contraction from peak negative strain (PNS) and strain rate (PNSR); relaxation from peak positive (PNS) and strain rate (PPSR), and global strain (GS). LV diastolic function was assessed by E/A ratio, flow propagation velocity (FPV), E/FPV, S'D (from pulmonary vein flow), long-axis early diastolic velocity (E), and E/E'.

Methods: 64 subjects (21 ± 4 years, 44 male) were enrolled: 40 endurance athletes and control group of 24 age- and sex-matched sedentary subjects. LA geometry was assessed by volumes at the MVO (MVOV), MVC (MVCV), and at the beginning of the P wave (PV), while LA function by passive EF (E) as PV-MVCV/PV. LA deformation was measured by STI: contraction from peak negative strain (PNS) and strain rate (PNSR); relaxation from peak positive strain (PPS) and strain rate (PPSR), and global strain (GS). LV diastolic function was assessed by E/A ratio, flow propagation velocity (FPV), E/FPV, S'D (from pulmonary vein flow), long-axis early diastolic velocity (E), and E/E'.

Results: Athletes had 'supranormal' LV diastolic function (E/A=2.3±0.5 vs 1.5±0.2; PV74±14 to 37±9 cm/s; E/FPV=1.3±0.7 vs 1.8±1.1, S'D=0.7±0.2 vs 1.3±0.1; E=1.4±0.2 vs 2.5±0.2, all p<0.05). There were changes in LA geometry and optimized LA deformation in athletes (see table). Univariate analysis showed that GS was correlated with E, E' and FPV (r=0.71; r=0.52; and r=0.58, all p<0.05). There were significant negative correlations between BNP and 3DRAEF (r=0.39, p<0.01; all other events occurred at the same time in both chambers. LA S and SR had higher absolute values compared with corresponding LV S and SR values (p=0.001 for all). SA correlated with changes in LA length (r=0.39, p=0.006) and volume (r=0.30, p=0.003) during LA contraction. LA Sa correlated with changes in LA length (r=0.63, p<0.001) and volume (r=0.44, p<0.001) during LV contraction. Multiple stepwise regression analysis revealed that the single most important independent predictor of LA Sa and SR was the corresponding LV Sa and SR. This was also true during A contraction (r=0.33, p=0.01) when compared with the events during LV contraction and LV early relaxation (r=0.5, r=0.27). Additionally, LA Sa, SrA and SreA were also predicted by LA end-diastolic volume. There was no significant correlation between LA Sa and SR during LA contraction, LA wave and LV volume at P-wave onset, LA and LV EDV; between LA SaS and SR and LV and LV volume at P-wave onset; between LA Sa and E, and LV and LV on wave onset; between LA SaS and E, and LV and LV on wave onset; and between LA SaS and LV SW and Ea.

Conclusions: There is substantial interaction of LA Sa and SR on the corresponding LV S and SR through the shared mitral annulus, most pronounced when the LV is the driving chamber. Thus, STE may be useful to assess only the LA booster function, rather than assessing intrinsic LA reservoir and conduit function, because of its less dependence on corresponding LV S and SR during LA contraction.

Detection of pulmonary congestion using the newly-developed pocket-sized transthoracic echocardiographic imaging device in patients with suspected heart failure

Background: Ultrasound lung comets (ULCs) assessment is simple, fast, and clinically useful for the evaluation of pulmonary congestion in patients with heart failure (HF). Recently-developed pocket-sized transthoracic echocardiographic (pTTI) imaging device has allowed physicians to perform screening study in a variety of clinical settings. The aim of this study is to investigate the feasibility and usefulness of pTTI for the evaluation of ULCs in patients with HF.

Methods: This prospective study consisted of 51 consecutive patients (25 female, 66±15 years) with known or suspected HF who underwent the standard TTE (sTTE) and pTTI. Exclusion criteria included the following: patients with hemodynamics, recent cardiac surgery, known pulmonary diseases. The examination of pTTE was performed with the Vscan (GE Medical Systems). Immediately after pTTE study including the assessment of ULCs, all patients underwent sTTE and pTTE assessment by another sonographer blinded to the results of pTTE study. We defined ULC score according to the number of ULCs observed in each segment (right upper & lower, left upper & lower) of chest wall as follows: None: 0, Mild (the number of ULCs: 0-5); 1, Moderate (6-10); 2, Severe (11-3). The sum of these scores in each 4 segments is defined as total ULC score (0-12 points). Clinical diagnosis of congestive HF was based on the Framingham criteria, with all corroborative information reviewed by 2 cardiologists blinded to the information of ULCs examinations by pTTE. The patients with ULCs had lower left ventricular (LV) ejection fraction and larger IVC diameter, left atrial volume index. BNP values were also well correlated with ULC score evaluated by pTTE (r=0.60; Spearman, p<0.0001). Receiver Operating Characteristic (ROC) curve analysis revealed the relationship between ULC score evaluated by pTTE and the diagnosis of HF (AUC: 0.93). The ULC score of 2 was found to maximize the diagnostic accuracy with a sensitivity of 88% and a specificity of 83%. The ULC score of 4 had a sensitivity of 60% and a specificity of 100%.

Conclusion: Detection of pulmonary congestion using the newly-developed pTTI imaging device in patients with HF is feasible and accurate.
Effect of through plane motion for the accuracy of
Diagnostic accuracy and cost-effectiveness of pocket-sized transthoracic echocardiography

M. Takeuchi, K. Otsuji, Y. Otsuji; University of Occupational and Environmental Health, School of Medicine, Kitakyushu, Japan

Purpose: Measurements of 2D circumferential strain (CS) is affected by loss of speckles due to through plane motion, raising the doubt regarding its accuracy. 3D speckle tracking echocardiography (STE) may eliminate this limitation. If through-plane motion affects 2D speckle tracking analysis, we hypothesized worst correlation and largest mean difference of CS were observed at basal level, and best correlation and least difference of CS were noted in the apical level between 2DSTE and 3DSTE measurements.

Methods: We obtained 2D basal, mid and apical short-axis images, and 3D full-volume datasets (GE, Vivid E9) in 44 patients with various cardiovascular disease (mean age 62±19 years, 23 men). Using 2D/3D speckle tracking software, segmental CS at end-systole was measured. Global CS and average CS at each of 3 LV short-axis levels were calculated in both modalities. Using anatomical M-mode, we measured mitral annular displacement (MAD) on apical 4-chamber view, and patients were divided into two groups according to the median value of MAD (9.4mm) for investigating the effect of through plane motion.

Results: Although a good correlation of global CS was noted between the two methods (r=0.80, p<0.01), mean values were significantly higher in 3DSTE compared to 2DSTE (-18.4±6.3 vs. -14.7±5.0, p<0.001). Correlation of averaged CS and their mean bias between the two methods were 0.66±0.61 at basal level, 0.78±0.17 at mid level, and 0.60±0.23 at apical level, respectively. Correlation of global CS between the two methods was higher in group of patients who showed MAD less than 9.4mm (r=0.81) compared to group of patients with MAD > 9.4mm (r=0.61).

Conclusions: Our results suggest that through plane motion affects CS measurements using 2DSTE, especially in subjects with normal longitudinal function.
Results: A total of 104 patients were studied. There was excellent agreement between the Vscan and the high-end echocardiograph for left ventricular systolic function and pericardial effusion (Kappa 0.89 and 0.81 respectively), and agreement was good or moderate for evaluating aortic, mitral and tricuspid valve function and left ventricular size (Kappa 0.55-0.66). Visualization of the Vscan images in full-screen format on a PC did not in general confer added value.

Conclusion: The Vscan used by a trained cardiologist has good diagnostic accuracy in the emergency setting compared to a high-end echocardiograph, despite small screen size and lack of pulse-wave and continuous Doppler.

Table 1. Inter-vendor variabilities

<table>
<thead>
<tr>
<th>V1</th>
<th>V2</th>
<th>Bias (95% LOA)</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRS</td>
<td>53.7±10.7</td>
<td>–37±9.1†</td>
<td>0.18</td>
</tr>
<tr>
<td>GLS</td>
<td>–21.7±2.3</td>
<td>–19.7±2.7†</td>
<td>0.63</td>
</tr>
<tr>
<td>V1</td>
<td>V2</td>
<td>Bias (95% LOA)</td>
<td>ICC</td>
</tr>
<tr>
<td>GRS</td>
<td>53.6±10.4</td>
<td>–32±8.6</td>
<td>0.02</td>
</tr>
<tr>
<td>GLS</td>
<td>–21.4±1.8</td>
<td>–19.8±2.4†</td>
<td>0.31</td>
</tr>
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</table>

Conclusions: 2DSTE-derived LV strain measurements are highly vendor-dependent. Due to a low inter-vendor agreement, 2D strain data are not interchangeable when conducting a longitudinal follow-up or across-sectional assessment of the LV myocardial deformation.

Usefulness of automated function imaging to detect myocardial ischemia during dipyridamole stress echocardiography

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Purpose: Dipyridamole stress echo (DSE) is currently used as an alternative to dobutamine stress echo in detecting coronary artery disease (CAD). However, the lower sensitivity, especially in single-vessel disease and the high inter-observer variability of wall motion (WM) analysis are two major drawbacks of DSE. We aimed in this study to investigate the usefulness of global longitudinal strain (GLS) by automated function imaging (AFI, Echopac GE Horten, Norway) to improve diagnostic accuracy and reproducibility of DSE in detecting myocardial ischemia.

Methods: 37 patients (18 men, 67±9 years), with intermediate/high pre-test CAD probability, underwent DSE followed by coronary angiography within one week. Diagnostic accuracy in the identification of CAD, evaluated through sensitivity, specificity and positive/negative predictive values (PPV/NPV), was analyzed for mean wall motion score index (WMSI) and GLS. Optimal cutoff value to define normal GLS was -20%. Concordance between each diagnostic method and the reference standard, represented by coronary angiography, was evaluated by kappa score and Kendall’s tau coefficient. Furthermore, the agreement between two observers with different experience in DSE was assessed by using Cohen’s k coefficient.

Results: Prevalence of significant CAD (more than 50% of luminal narrowing) was 70% and prevalence of single vessel disease was 60%. Mean GLS significantly decreased from rest (+17±4%) to peak DSE (+15±4%; p<0.001). Sensitivity, specificity, PPV and NPV for WMSI were respectively: 50%, 67%, 83% and 29%. However, combination GLS and WMSI had the highest sensitivity (70%), specificity (70%), PPV (87.5%) and NPV (40%). Furthermore GLS showed higher concordance with coronary angiography (k = 0.75; Kendall’s tau = 0.78) than WMSI (k = 0.11; Kendall’s tau = 0.14). In addition, there was a good agreement between a trainee and an expert observer by using GLS in comparison with WM analysis for images interpretation at rest (k = 0.61 for WM, k = 0.57 for GLS) whereas the agreement significantly improved for images interpretation at peak stress (k = 0.50 for WM, k = 0.70 for GLS).

Conclusions: Combination of GLS and WMSI resulted in significant increase in the accuracy of DSE to detect myocardial ischemia, especially with regard to the test sensitivity. Besides, GLS analysis provides an increase of the agreement for images interpretations between experienced and non-experienced observer, especially at peak stress. Hence, adding routinely GLS analysis during DSE could probably be helpful for more accurate patient risk stratification.

Changes in left ventricular strain during exercise stress echocardiography in healthy subjects: a speckle tracking echocardiography study

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Background: Stress echocardiography is widely used but its major limitation is the subjective interpretation of wall motion changes. Speckle tracking echocardiography (STE) offers a quantitative method with the semiautomatic evaluation of the different components of myocardial deformation. The aim of our study was to evaluate changes in left ventricular (LV) systolic performance during the different steps of exercise stress echocardiography (ESE) in a population of healthy subjects.

Methods: ESE was performed in 25 healthy subjects (mean age 26±3.1) in the semi-supine position on a tilted cycleergometer. The workload was increased every 2 minutes by 25W, up to the achievement of 100W. Echo was performed at each stage of the physical exercise and during the recovery phase. LV global longitudinal strain was calculated averaging values of all myocardial segments in apical 2-, 3- and 4-chamber views; radial, circumferential and strain LV twistng were obtained from the parasternal short-axis views at basal and apical levels.

Results: Mean heart rate of 164±21 bpm was reached. All LV parameters explored increased significantly, reaching the maximum value at peak exercise. Subjects showed a relative increase of strain values respect to baseline of 48±14.1% for LV global radial strain (baseline: 23.9±8.6; peak value: 35.4±10.1%); 43.8±12.2% for LV twisting baseline: 10.5±3.6; peak value: 15.5±4.7%; 34.9±8.6% for global circumferential strain (baseline: 24.3±6.6; peak value: 32.8±9.6%) and 13.4±4.9% for global longitudinal strain (baseline: 20.1±2.9; peak value: 22.8±2.8%).

Conclusions: This is the first study that reported the normal range values and the percentages of increment of LV strain that physiologically occurs during ESE, fixing a reference point to better interpret pathological studies.
Hypertrophic cardiomyopathy in Iceland: MYBPC3 founder mutation?

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The aim of this study was to investigate Hypertrophic Cardiomyopathy (HCM) in Iceland, identify sarcomeric mutations causing HCM and understand the phenotype consequences of these mutations. Iceland, an island with the population of 300,000 offers a great opportunity to investigate this heterogeneous disease in a whole population.

Methods: The study cohort consisted of all patients having clinical diagnosis of HCM in Iceland from 1997-2010. Patients were searched through medical records and echocardiographic database at the main hospitals and cardiologists private clinics. All HCM patients were invited to have genetic testing and an interview. Samples were screened for the MYBPC3 c.927-2A→G mutation previously described in two Icelandic families. If negative, targeted sequencing of 8 HCM genes and the GLA gene was performed. Information on phenotype and clinical data were obtained from patient medical records and interviews.

Results: 177 patients with HCM diagnosis were identified, 156 were alive and 12 had already been genotyped and 119 accepted to participate in the study. 72 (55%) had the c.927-2A→G mutation in MYBPC3. Additionally, 4 had other variants in MYBPC3, one was diagnosed with a variant in MYH7. 5 were diagnosed with variants in the GLA gene. Fabry disease has been confirmed in three of these patients. Clinical data on patients with c.927-2A→G mutation in MYBPC3 are shown in the table. 1

<table>
<thead>
<tr>
<th>Age at diagnosis (mean, range)</th>
<th>40.4 (7-72)</th>
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<tbody>
<tr>
<td>Average LV thickness (mm)</td>
<td>21.7</td>
</tr>
<tr>
<td>Adverse cardiac event</td>
<td>11 (15.3%)</td>
</tr>
<tr>
<td>Age at first adverse event</td>
<td>51 (17-72)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>12 (16.7%)</td>
</tr>
</tbody>
</table>

All HCM cases are offspring of a common ancestor. We expect from inheritance studies, that he/she lived more than 5 generations ago.

Conclusion: The c.927-2A→G mutation in MYBPC3 is the leading cause of HCM in Iceland, accounting for 55% of cases. The c.927-2A→G mutation causes serious disease with an average age of onset of 40 yrs. We hypothesize that all 72 individuals with the c.927-2A→G mutation are offspring of a common ancestor. At present, we cannot estimate when this common ancestor lived in Iceland, but we expect from inheritance studies, that he/she lived more than 5 generations ago.

Hypertrophic cardiomyopathy in muscular dystrophy: genetically caused structural weakness vs. acquired myocarditis? Answers based on a siblings study


Background: Muscular dystrophy type Duchenne (DMD) and type Becker (BMD) represent the most common X-linked genetic diseases. Apart from progressive proximal skeletal muscle weakness, DMD and BMD are characterised by cardiac muscle involvement with a characteristic pattern of myocardial damage affecting the subepicardium of the left ventricular (LV) free wall. The molecular pathomechanism leading to cardiomyopathy is still unclear: the fragility of the cell membrane caused by genetically deficient dystrophin – may predispose cardiomyocytes to cell death in response to mechanical stress. However, it is also argued that DMD/BMD patients may be more susceptible to myocarditis which in turn may also cause subepicardial damage in the LV free wall. In order to further elucidate the role of myocarditis, we evaluated cardiac magnetic resonance (CMR) studies of DMD/BMD siblings of the same age group.

Methods: Since 2007, we have performed cardiac examinations comprising (amongst others) comprehensive CMR studies in more than 120 patients with DMD and BMD. The CMR studies comprised (amongst others) cine-CMR and T1-weighted late-gadolinium-enhancement (LGE) imaging in order to assess functional and structural parameters. In order to enable a meaningful comparison of CMR study results, we selected only those DMD/BMD siblings who were at least 12-year (DMD) or 20yrs (BMD) old and in whom the difference of age was less than 10yrs.

Results: Four pairs of siblings were identified (with each sibling having the same dystrophin gene mutation) fulfilling the inclusion criteria. The age of sibling pair no.1 (BMD) was 21yrs and 24yrs, left ventricular ejection fraction (LV-EF) was 45% and 39%, and the extent of LGE was 2.8% and 2.6%, respectively. The age of sibling pair no.2 (BMD) was 36yrs and 38yrs, LV-EF was 36% and 42%, and the extent of LGE was 4.1% and 3.3%, respectively. The age of sibling pair no.3 (BMD) was 29yrs for both (monozygous siblings), LV-EF was 65% and 66%, and the extent of LGE was 0.5% and 1.1%, respectively. The age of sibling pair no.4 (BMD) was 40yrs and 43yrs, LV-EF was 58% and 63%, and the extent of LGE was 3.7% and 5.1%, respectively. All siblings demonstrated the same localization of LGE in the subepicardium of LV free wall (= septal wall).

Conclusions: The similar results in LV-EF, extent of LGE and localization of LGE in siblings with the same dystrophin gene mutation clearly suggest that the fragility of the cell membrane caused by genetically deficient dystrophin – but not acquired myocarditis(?) – is the cause of the characteristic cardiomyopathy in DMD/BMD patients.

Phenotype-genotype correlation in patients with mutations in the beta-myosin converter domain

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Purpose: Our main purpose was to evaluate the genotype-phenotype correlation of mutations located in the beta-myoisin converter domain. This region, located between aminoacids 2799 and 2777, is responsible for the elastic distortion of the protein which allows strain to develop within the motor before the cargo is actually moved. Several mutations affecting this important and highly conserved region have previously been described. Several mutations affecting this important and highly conserved region have previously been described.

Methods: Identification of mutations in the converter domain on MYH7 was performed in a cohort of more than 800 cases diagnosed either with Hypertrophic (HCM) or Dilated-Cardiomyopathy (DCM). Additionally, we reviewed the published data about all missense mutations located within this domain.

Results: In our centre, mutations were identified in 11 families comprising 59 relatives and 30 carriers, all diagnosed with HCM except 1 family (LVNC and DCM). These mutations were G716R (2 families), G741R (1 family), G676R (1 family), 1573N (1 family, novel mutation), 1736E (5 families) and R179Q (1 family). Taking in account our data and data from literature, a total of 21 pathogenic missense mutations have been identified within this domain. They were distributed in 143 families comprising 470 relatives (in half of those families more than 1 member was diagnosed). Of these relatives, 424 were affected or possibly affected (11 of them diagnosed with DCM and the rest with HCM) and 382 were mutation carriers. We observed an early onset of disease with a mean age at the diagnosis of 27±18 years (range 1 to 77, 56% males). Thirteen of 21 mutations were associated with a severe adverse event affecting at least one member in 52/143 families (36%). These serious events occurred in 151 affected or possible affected relatives (36%), distributed as follow: sudden death occurred in 96 patients (22%, 6% and at least 54 of them were younger than 45 years old, heart failure death in 35 (8.2%), cardiac transplantation in 18 (4.2%) and fatal stroke in 6 (1.4%). Finally, 61 patients (16%) presented an impairment in the left ventricular systolic function.

Conclusions: Data from our families and from the extensively reviewed publications indicated that mutations located within the beta-myoisin converter domain presented an early onset of disease. A significant proportion of mutations were associated with the occurrence of a severe adverse event and also left ventricular dysfunction, in a high proportion of families.

Is the gene MYOM2 encoding myomesin 2 involved in the pathogenesis of hypertrophic cardiomyopathy?

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Background: Hypertrophic cardiomyopathy (HCM) is the most frequent genetic myocardial disease with a prevalence 1/500. Although twenty mostly sarcomeric genes have been shown to cause HCM, it is anticipated that additional so far unknown disease genes exist. In a candidate gene approach, we did a genetic screening of myomesin 2 (MYOM2), a M-band protein expressed in cardiac sarcomeres.

Methods: We clinically evaluated a cohort of fifty-eight HCM patients on the basis of medical history, physical examination, echocardiography, and 12-lead ECG, after obtaining informed consent. Using PCR and direct automated Sanger sequencing, the thirty-six coding exons of MYOM2 were analyzed. The study was approved by the institutional review board of the Charité.

Results: As expected, a number of known single nucleotide polymorphisms (SNPs) were detected. Interestingly, we identified three novel mutations (M269T, S466R, R1079X) in three unrelated HCM patients. All mutations were heterozygous and were not detected in controls. Furthermore, they are not registered in the SNP database, although more than 200 variations are known in MYOM2. The mutations affect different domains of the protein. Whereas the affected residue of codon 269 is highly conserved in different species from chimp to fish, the codon 269 was conserved only in mammals. While M269T and S466R are missense mutations affecting one residue, the mutation R1079X created a premature stop and is predicted to lead to a truncated protein from immunoglobulin-like domain 10. The two most common HCM disease genes, MYH7 and MYBPC3, as
well as a number of other disease genes (MYL2, MYL3, ACTG, TNNT2, TNN3, TPM1, TNNC1, CSRPT3) showed no mutation in this HCM cohort. Notably, the phenotype of the three identified patients was characterized by left ventricular outflow tract obstruction and arrhythmias which lead in one of them to an ICD implantation. The examination of the families is underway.

Conclusions: According to Mendelian inheritance in man, MYOM2 was not considered as the cause for the patient’s disease so far. We could detect the first three novel mutations in that gene in HCM patients. Our data suggest that MYOM2 may be involved in the pathogenesis of hypertrophic cardiomyopathy.

Unravelling mutation effects from secondary adaptations in cardiomyocytes of Familial Hypertrophic Cardiomyopathy patients

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Purpose: About 1/3 of genotyped FHC patients carry missense mutations in the β-cardiac myosin heavy chain (β-MHC). Yet, at the sarcomere level of cardiomyocytes, the primary functional effects of these mutations are still largely unknown. We aimed to characterize the effects of the highly malignant β-miomyosin heavy chain (β-MHC) missense mutation R722G in myocardial tissue and to compare the data with previous findings in M. soleus fibers with the same mutation. This allows to differentiate (1) the primary functional effects of the mutation and (2) adaptational processes in the myocardium.

Methods: In left ventricular cardiomyocytes from explanted hearts of patients with the β-miomyosin mutation R722G and in donor cardiomyocytes we determined force generation, force-calcium relations, and crossbridge kinetics. We also determined the relative expression of mutated vs. wildtype β-MHC at the mRNA- and protein level and analyzed the phosphorylation of sarcomeric proteins. To assess cardiomyocyte structural properties, histology and electron microscopy was also performed.

Results: Measurements revealed reduced maximum force generation but unchanged calcium-sensitivity of the myocytes. Yet, previous studies on slow skeletal muscle fibers with the same mutation showed reduced calcium-sensitivity and increased maximum force. The expression of mutated β-MHC-mRNA and β-miomyosin in LV tissue was found to be 68% and 64% of total β-MHC-mRNA and β-miomyosin, respectively, which is the same fraction as in M. soleus. Gel electrophoresis of the HCM cardiac tissue showed reduced phosphorylation of tropoactins I and T, miomyosin binding protein C, and miomyosin light chain 2 compared to donor tissue, which is similar to previous findings for failure human heart. Treatment with protein kinase A (PKA) to adjust phosphorylation of TnI and MyBP-C in donor and HCM patient cardiomyocytes was characterized by left ventricular cardiomyocytes with the same mutation showed reduced calcium-sensitivity due to changes in protein phosphorylation. (2) To identify primary functional effects of a mutation in myocardial tissue at an advanced stage of the disease, posttranslational modifications like protein phosphorylation and ultrastructural alterations must be taken into account.

Conclusions: (1) The primary effects of HCM related mutations might obscure typical adaptations commonly seen in end stage heart failure like increased calcium-sensitivity due to changes in protein phosphorylation. (2) To identify primary functional effects of a mutation in myocardial tissue at an advanced stage of the disease, posttranslational modifications like protein phosphorylation and ultrastructural alterations must be taken into account.

Lamin A/C mutation is independently associated with an increased risk of arterial and venous thromboembolic complications

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Purpose: Lamin A/C (LMNA) mutation carriers suffer from a variety of clinical phenotypes, including dilated cardiomyopathy (DCM). Although it has been suggested that carriers are at risk for thromboembolic complications, it is unknown whether this risk is higher than can be expected from the underlying cardiac abnormalities.

Methods: We compared a cohort of 76 LMNA mutation carriers with a cohort of 984 DCM patients without a LMNA mutation, with respect to the prevalence of arterial and venous thromboembolic complications. Furthermore, we carried out a case-control study to explore whether a prothrombotic phenotype was present in LMNA mutation carriers without DCM or atrial tachyarrhythmias (n=14) and compared this with mutation negative relatives (n=13).

Results: The prevalence of thromboembolic complications was higher in the cohort of LMNA mutation carriers than in DCM patients (22 vs 11%, p<0.05), after adjusting for mean follow-up of 42.2±12 and 49.8±12 years. After adjustment for possible confounders, including atrial tachyarrhythmias and left ventricular ejection fraction, LMNA mutation carriership was independently associated with an increased risk of thromboembolic complications (HR 4.8, 95% CI: 2.2-10.6).

Conclusions: LMNA mutation is independently associated with an increased risk of arterial and venous thromboembolic complications. Laboratory research in LMNA mutation carriers without severe cardiac abnormalities suggests a prothrombotic phenotype.
these mutations were found in healthy subjects. Immunohistochemical analysis of endomyocardial biopsies demonstrated an abnormal distribution of myopalladin in cardiac myocytes from the p.P961L mutation carrier, while the periodic localization of myopalladin in sarcomeres was unchanged in the p.R955W carrier and four other DCM patients used as controls. Interestingly, in cardiac myocytes from the p.P961L patient we also observed a disturbed localization of α-actinin, which is a known binding partner for myopalladin. In the ANKRD1 gene we identified only one novel synonymous mutation in a DCM patient, which was a mononucleotide substitution in exon 2 (c.108C>T), but failed to detect non-synonymous mutations.

Conclusions: Taken together, we have identified novel point mutations in the third immunoglobulin-like domain of myopalladin. One of these missense mutations, a substitution of a highly conserved prolyl residue in position 961, was associated with structural alterations in the sarcomere organization. These findings point to the role of myopalladin in myofibrillarlogenesis with impact on the pathogenesis of diluted cardiomyopathy.

P4874 Tei index, a useful indicator for right ventricular involvement in fabry disease
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Aim: Fabry disease is an X-linked lysosomal storage disorder caused by a deficiency of α-galactosidase A. Besides renal failure and strokes, cardiomyopathy and cardiac arrhythmias are frequent complications of the disease. The cardiomyopathy can be characterized by left and right ventricular hypertrophy and cardiac fibrosis. The Tei index, a marker for combined diastolic and systolic function, has been investigated in Fabry disease to assess left ventricular dysfunction and correlates with left ventricular hypertrophy. Whether right ventricular involvement is accompanied by systolic and diastolic dysfunction in Fabry patients is as yet unknown. The aim of this study was to investigate if right ventricular hypertrophy is accompanied by right ventricular dysfunction, using Tei index.

Methods: A total of 83 (30 males, mean age 43 years) genetically confirmed consecutive Fabry patients and 21 (9 males, mean age 43 years) healthy controls were included in this study. Standard echocardiography was performed in all patients, including TEI-index of the lateral annulus off the right ventricle, right ventricular mass index (RVMI), tricuspid annular plane systolic excursion (TAPSE) and tricuspid lateral annular systolic velocity (Sa). 49 Patients receiving enzyme replacement therapy (ERT) and 34 patients had natural history.

Results: TAPSE (22.6 ± 0.8) and Sa (12.4 ± 0.4) were significant lower in the Fabry patients compared controls (TAPSE 24.8 ± 1.63, p<0.001, Sa 13.6 ± 0.8, p <0.001). The TEI-index was significantly higher in the Fabry patients (0.51 ± 0.03) compared to the controls (0.28 ± 0.03, p<0.001). The LVMI was significantly higher in the Fabry patients (124.8 ± 11) compared to the controls (94.8 ± 7, p<0.001). The TEI-index of the right ventricle correlated significantly with LVMI and the TEI-index (r 0.542, p<0.001).

Conclusion: In comparison to healthy controls, Fabry patients display right ventricular dysfunction as measured by TEI-index. The right ventricular dysfunction correlates to the degree of left ventricular hypertrophy.

P4875 Role of serum NT-proBNP measurement in the diagnosis of early cardiac involvement in patients with Anderson-Fabry disease
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Purpose: NT-proBNP has an established role in the diagnostic and prognostic assessment of heart failure. Cardiac involvement in AFD is common, however detection of early disease is challenging. The aim of this study was to determine the relation between serum NT-proBNP concentration and cardiac abnormalities in patients with Anderson Fabry disease (AFD).

Methods: NT-proBNP was measured under resting conditions in 117 patients with AFD (48 ± 15 years old, 46.2% male). All patients underwent clinical evaluation including ECG and echocardiogram.

Results: NT-proBNP concentrations ranged from <5pmol/L to 6059pmol/L. Eighty six (74%) patients had cardiac involvement (defined as an abnormal ECG or echocardiogram). A cut off of >250pmol/L had a 69% sensitivity and 94% specificity for detecting cardiac involvement in AFD with area under a receiver operator characteristics curve of 0.85 (95% CI 0.79-0.92). In multiple regression analysis the following were independently associated with logNT-proBNP levels: age, creatinine, LA volume index, E/Ea and the presence of an abnormal ECG (R2 = 0.67, p < 0.05).

Conclusion: NT-proBNP concentrations are raised in patients with Anderson-Fabry disease and cardiac involvement and correlate with non-invasive markers of diastolic dysfunction. These findings suggest that measurement of NT-proBNP may assist in decisions on the timing of enzyme replacement therapy.

P4876 Advanced left heart disease in cystic fibrosis: a distinct form of cardiomyopathy
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During decades, occasional cases of cardiomyopathy (CMP) have been described in patients with cystic fibrosis (CF). Necropsies of children with CF who died of sudden death showed dilated left ventricles with patchy fibrosis. Currently, patients with CF usually reach adulthood, and the incidence and features of CMP in them are unknown.

Methods: We describe cardiologic findings of 9 adult patients with CF and left ventricular (LV) systolic dysfunction, 3 of them referred to our centre for cardiac transplantation and 6 found in a study of 120 CF patients without cardiac transplantation. We report data of clinical evaluation, blood tests, ultrasound and magnetic resonance (MRI) studies. Histological findings of the three explanted hearts are described. The remaining 114 patients without CMP served as control group.

Results: The mean age of the 9 CMP patients was 31 ± 7 years and 6 were male. Four of them had del508 mutation and 2 had a rare mutation of other CF-related genes. Their mean LV ejection fraction was 36% (vs 66 ± 8% in controls, p < 0.01); 55% had also diastolic dysfunction (vs 5% in controls, p < 0.01). Four patients (44%) showed moderate mitral regurgitation. Right ventricle was affected in 1 patient (11%) and was normal in all control patients. Mean NT-proBNP in CF patients with CMP was 1498 ± 3219 pg/ml (vs 58 ± 45 pg/ml in controls, p < 0.001). MRI showed a patchy delayed myocardial gadolinium uptake in 43% of CMP patients, vs 0.04 among controls, p < 0.05. Pathology of the 3 hearts explanted at transplantation showed patchy myocardial fibrosis in all cases, a finding similar to the autopsies of Keshan syndrome (CMP due to selenium deficiency). Eight patients (89%) with CMP had pancreatic exocrine deficiency, needing high-dose pancreatic enzyme supplements (vs 50% in the control group, p < 0.05), and 6/7 (87%) had a body mass index < 20 kg/m2 (vs 53 among controls, p > 0.07). From the pulmonary standpoint, the mean FEV1 for the 9 patients was 45 ± 16% (vs 60 ± 20% for controls, p > 0.08). All of them had a permanent airway colonization by Pseudomonas (vs 58% among controls, p > 0.04). In fact, 4/9 (44%) patients with cardiac involvement required lung transplantation (vs 1% in controls, p < 0.05).

Conclusions: A small percentage of adult CF patients show a distinct CMP with a characteristic patchy myocardial fibrosis, a finding similar to the autopsies of children with CF and other malnourishment syndromes. CMP should be suspected in CF patients with significant malnutrition and more severe pulmonary involvement. ProBNP levels could serve as a screening tool for this form of CMP.

P4877 Cardiac autonomic nervous system dysfunction in a cardiomyopathy mouse experimental model
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Purpose: Desmin is the major muscle specific intermediate filament protein.
Desmin null mice (des-/-) develop dilated cardiomyopathy with myocardial de-
genereation, extensive calcification and fibrosis which leads to arrhythmias and sudden cardiac death. Our aim was to investigate the cardiac autonomic nervous system function in the des-/- mouse by measuring heart rate variability (HRV) indices.

Methods: We generated des-/- mice by gene targeting via homologous recom-
bination in 129Sv genetic background. Twenty four hours ECG recordings were
obtained from 6m old des-/- and wild type (WT) mice, using a telemetry sys-
tem (DSI) and all RR intervals were recorded. The following linear and non-linear
HRV indices were calculated: Approximate Entropy (ApEn) modified to avoid self-
ocurrences, Detrended Fluctuation Analysis (DFA) and the beta-Spectral Expo-
nent. Poincare map measures were used to extract 3D measures of spread and
maximum and the 2D distances axis so1 and so2. Time domain (SDNN, SDNNi,
RMSSD, pNN50) and frequency domain (LV, HF) indices were also calculated.

Results: Results are presented in Table 1.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>WT (n=15)</th>
<th>des-/- (n=12)</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>ApEn</td>
<td>0.75±0.10</td>
<td>0.56±0.12</td>
<td>0.2</td>
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<tr>
<td>Beta-SE</td>
<td>0.94±0.08</td>
<td>0.61±0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>DFA_so2</td>
<td>0.89±0.06</td>
<td>0.72±0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>3Dmax</td>
<td>21.96±31.27</td>
<td>39.12±57.56</td>
<td>0.04</td>
</tr>
<tr>
<td>so1</td>
<td>3.79±0.74</td>
<td>8.48±1.88</td>
<td>0.02</td>
</tr>
<tr>
<td>LF</td>
<td>0.009±0.0007</td>
<td>0.001±0.0004</td>
<td>0.01</td>
</tr>
<tr>
<td>HF</td>
<td>0.006±0.0001</td>
<td>0.002±0.0001</td>
<td>0.03</td>
</tr>
<tr>
<td>SDNN</td>
<td>0.012±0.0011</td>
<td>0.016±0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>SDNNi</td>
<td>0.004±0.0001</td>
<td>0.011±0.0002</td>
<td>0.02</td>
</tr>
<tr>
<td>RMSSD</td>
<td>0.005±0.0001</td>
<td>0.012±0.0003</td>
<td>0.02</td>
</tr>
<tr>
<td>pNN50</td>
<td>0.31±0.12</td>
<td>1.58±0.56</td>
<td>0.02</td>
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</tbody>
</table>

Conclusion: Desmin null mice show a global autonomic nervous system dys-
function which affects both the sympathetic and the parasympathetic compo-
nents. This may explain the presence of arrhythmias and sudden cardiac death in
these mice. Further investigation is needed so as to clarify whether this dysfunc-
tion is a result of the extended myocardial fibrosis and calcification caused by the
absence of desmin.

MYOCARDITIS

P4878

Left ventricular mechanics in acute myocarditis

Correlation of 2D speckle tracking deformation and rotation imaging with troponin release and cardiac magnetic resonance findings


Background: Acute myocarditis with normal ejection fraction (EF) represents a diagnostic challenge for conventional echocardiography. Cardiac magnetic reso-
nance imaging (CMRI) is the current non-invasive reference standard for diag-
nosis. Speckle tracking imaging (STI) allows measurement of left ventricular (LV) torsion and deformation. Abnormalities of these parameters may contribute to
earlier diagnosis of myocardial inflammation.

Aim: The purpose of this study was to explore the longitudinal, circumferential, and
torsional mechanics of the LV in patients with acute myocarditis.

Methods: Longitudinal, circumferential and torsional mechanics of the LV were
quantified in 30 patients with myocarditis confirmed by cardiac MRI based on
clinical, laboratory and CMRI findings and 50 healthy age-matched controls. All
patients had chest pain, abnormal ECGs and preserved EF (>45%) whereas
coronary artery disease was angiographically excluded.

Results: In comparison with controls, global longitudinal strain values in myocarditis group (-17.35±3.08% vs. -20.0±2.63%, p<NS) were not sta-
tistically different, reflecting the preserved longitudinal contractility. On the
contrary, myocarditis patients showed decreased LV torsion (10.3±4.92 vs
14.28±4.30 degrees, respectively, p<0.001), apical rotation values (4.74±3.77
vs 8.73±2.85 degrees, respectively, p<0.003) and circumferential strain in the
mid posterior (-7.5±4.9% vs -16±4.7%, p<0.001), mid lateral (-7.1±7.3% vs
16.4±11%, p<0.001) and mid inferior wall (-15.4±6.9% vs -20.5±4.7%, p<0.001)
compared to controls. Tropin elevation was found in 25 patients (50%) with mean values 14.8±23.79 mmol/ml and was correlated with both LV tor-
sion (r=0.584, P=0.001) and the number of affected segments in CMRI (r=0.57,
p=0.04). A circumferential strain cut off below -12.5% for mid lateral and below
-10.5% for mid inferior segment yielded a sensitivity of 75% & 87.5% and a
specificity of 60% & 60% respectively, in predicting late enhancement (LGE) at
CMRI in these segments.

Conclusion: STI assessment revealed abnormal LV torsion and circumferen-
tial strain in acute myocarditis. Torsion impairment was strongly correlated to
the level of troponin release. On the contrary, longitudinal strain and conven-
tional echocardiographic parameters were not significantly affected. Circumfer-
ential strain yielded only modest specificity in predicting the segments with LGE
at CMRI
In vivo delivery of adenoviral vector containing interleukin-17 receptor A reduces cardiac remodeling and improves myocardial function in CVB-3-induced chronic myocarditis

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Purpose: Th17 cells have been implicated in the pathogenesis of myocarditis. Interleukin (IL)-17A produced by Th17 is dispensable for viral myocarditis but essential for the progression to dilated cardiomopathy (DCM). This study investigated whether adenoviral transfer of IL-17 receptor A would reduce cardiac remodeling and dysfunction in chronic viral myocarditis.

Methods and Results: In a mouse model of Coxackievirus B3 (CVB3)-induced myocarditis, delivery of adenovirus containing IL-17 receptor A (Ad-IL17R:Fc) reduced IL-17A production and decreased the mortality compared with Ad-null treated mice, which was accompanied by down-regulation of ADAMTS-1, MMP-2, collagen subtypes I and III, and a reduction in fibroblasts in the heart, suggesting an important role of IL-17A in fibrosis. These effects of Ad-IL17R:Fc correlated with a decrease of Th17 cells in the spleen and heart, and a reduction of systemic TNF-α and IL-6 productions. In cultured cardiac fibroblasts, IL-17A induced expressions of ADAMTS-1, MMP-2, collagen subtypes I and III, and increased the proliferation of fibroblasts.

Conclusion: Th17 cell and IL-17A induces cardiac fibrosis through mediating extracellular matrix remodeling and fibroblast proliferation in chronic viral myocardi- tis and DCM. Thus, blockade of IL-17A by adenoviral transfer of IL-17 receptor A may represent an alternative therapy for chronic viral myocarditis and its progres- sion to DCM.

Relation between cardiac magnetic resonance criteria for acute myocarditis and biomarkers of inflammation and myocardial damage

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Purpose: Diagnostic cardiac magnetic resonance (CMR) criteria for acute myocardi- tis (“Lake Louise” criteria) have been recently proposed. In the setting of clinically suspected myocarditis, CMR findings are consistent with myocardial in- flammation, if at least 2 of the following features are present: 1) regional or global myocardial thickening or wall motion abnormalities; 2) pericardial effusion; 3) focal lesion of myocardial necrosis. Adverse outcomes were observed in association with non-ischemic regional distribution. Scarce data are however available regarding the relationship between these criteria and biochemical markers of inflammatory activity and myocardial injury.

Methods: A total of 26 consecutive patients (20 males, mean age 38.8±14 years) with diagnosis of acute myocarditis on the basis of clinical presentation (chest pain, dyspnea or palpitations, associated with recent gastrointestinal or respira- tory infection) and CMR “Lake Louise” criteria were included. For each patient, peak values of C-reactive protein (CRP) and cardiac troponin I (cTnI) were determined. In addition, the following CMR features were determined: 1) global myocardial signal intensity (SI) in T2W images, quantified by a SI ratio of myocar- dium over skeletal muscle (expression of myocardial oedema); 2) global myocar- dial early gadolinium enhancement (EGE) ratio between myocardium and skeletal muscle (expression of myocardial inflammation by concanavalin A or cardiac myosin in cultured lymph nodes (LN) cells from rats with myocarditis. The cytotoxic activities of LN cells from rats immunized with myosin and treated with Ig were reduced against cardiac myocytes and F-2 cells, compared with those treated without Ig. The adoptive transfer of myocarditis from LN cells of Lewis rats with myocarditis into severe combined immunodeficient (SCID) mice was successfully achieved. Treatment with Ig, but not with Fab(2) fragments of Ig, reduced the mortality and the sever- ity of myocarditis in SCID mice. Decreased ability of LN cells of Ig-treated rats, but not of Fab(2) fragments-treated rats, to transfer autoimmune myocarditis was also demonstrated.

Conclusion: Treatment with Ig ameliorated autoimmune myocarditis with induc- ing myosin unresponsiveness via the Fc portion, resulting in suppression of the Th1 cytokine production and the cytotoxic activities of LN cells, which operated to- gether in the development of autoimmune myocarditis.

Infectable collagen implant improves survival and early cardiac remodeling after fulminant myocarditis in rats

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Purpose: Acute myocarditis can lead to massive cell death, destruction of extra- cellular matrix, left ventricle (LV) dilatation, dysfunction and death. We sought to test the hypothesis that injection of collagen-based implant into the inflamed myocardium would stabilize LV and prevent adverse remodeling and dysfunction.

Methods and Results: Autimmune myocarditis was induced in 42 male Lewis rats. Fourteen days after immunization, sick animals were randomized into either injectable-collagen implant or saline injection, into anterior inflamed myocardium. LV remodeling and function were assessed by serial echocardiography and car- diac magnetic resonance (CMR) scans; before immunization, before collagen im- plantation and 17 days after implantation. Thirty one days after immunization rats were euthanized and subsequently underwent histopathological examination. Notably, 30 day survival rate was significantly higher in collagen-treated group compared with control (87.5% vs. 50%; p=0.03). CMR imaging of control ani- mals showed epicardial late gadolinium enhancement, as marker of fibrosis, LV wall motion abnormalities, and in some cases pericardial effusion. The injectable collagen implant increased systolic and diastolic wall thickness, 10 days after treatment, compared with control (p=0.07, p=0.05). Furthermore, while injectable collagen implant attenuated the LV systolic and diastolic dilatation and preserved LV ejection fraction, control animals developed significant LV dilatation (p=0.02, p=0.04) and dysfunction (p=0.01). However, these favorable effects disappeared within 17 days after treatment.

Conclusions: Injectable collagen implant improves survival in a rat model of fulminant myocarditis. However, while the effect on survival was sustained, the early protective effect on LV remodeling was limited to the early period after treatment.

Matrix Metalloproteinase-13 is beneficial in viral myocarditis not only by preventing cardiac inflammation but also reducing cardiac inflammation due to regulating chemokines

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Myocarditis is an important cause for cardiac failure especially in younger pa- tients followed by the development of cardiac dysfunction and death. The present study investigated whether gene deletion of matrix metalloproteinase-13, an im- portant collagenase in the heart, influences cardiac inflammation and remodeling in murine coxsackievirus-B3 (CVB3) induced myocarditis.

Methods and Results: MMP-13 knockout mice (MMP-13(-/-)) and their controls (WT) were infected with CVB3 to induce myocarditis and 7 days later LV func- tion was analyzed invasively. CVB3 induced significant cardiac inflammation (increased CD3 (+18 fold) and CD68 (+ 25 fold) cells) as well as cardiac dysfunction (decreased cardiac output (-24%) in WT CVB3 animals. Interestingly, deletion of MMP-13 increased the protein level of the chemokine MCP-1 (4 fold). This incre-
ment of a potent chemokine due to MMP13 KO aggravated cardiac inflammation (3 fold) as well as cytokine levels (increased TNF-alpha 6 fold and IL1 beta 3 fold) compared to infected WT animals. Moreover, this excessive cardiac inflammation lead to an increased transdifferentiation of fibroblasts to pathological activated myofibroblasts (10 fold), which are known to be induced by inflammatory cells. This was associated with detrimental cardiac remodeling leading to severe cardiac dysfunction when MMP-13 KO were compared to WT animals after CVB3 infection. Interestingly, also viral load was increased in MMP-13/- mice with significantly more cardiac apoptosis being present in the infected myocardium.

Conclusions: Loss of MMP-13 increased the inflammatory response and CVB3 infection, which impaired cardiac remodeling, apoptosis and function during CVB3 induced myocarditis due to an increment of the chemokine MCP-1. MMP-13, similar to other MMPs like MMP-2 might be more than just a degrada-
ton system for cardiac collagen but may modulate inflammation by processing chemokines as MCP-1 and therefore being one negative feedback loop in cardiac inflammation.

No evidence of adenoviral genome in endomyocardial secretome from mononuclear cells confers PCR assay of EMB specimens in patients with new-onset unexplained DCM. Infection does not seem to play an important role in the pathogenesis of new-onset unexplained DCM, which may have important therapeutic consequences. However, adenovirus infection was present in the myocardium of more than half of the patients with new-onset unexplained DCM.

Methods: In 58 consecutive patients (53±11 years, 42 men) with new-onset unexplained DCM (left ventricular ejection fraction 30±8%), endomyocardial biopsy (EMB) specimens were studied by immunohistochemistry (HILA expression) and polymerase chain reaction (PCR) techniques.

Results: The genome of cardiotropic infectious agent was found in EMB specimens from 14 patients (24%). Namely, Bb-genome was present in 13 subjects and parvovirus B19 in 6 (10%), enterovirus in 5 (9%), human herpes virus 6 in 5 (9%), cytomegalovirus in 3 (5%) and Epstein-Barr Virus in 2 (3%) patients. Adenovirus and herpes simplex virus 1 genomes were not detected in any subjects. Myocardial inflammation was found in 18 patients (31%), of whom in 7 subjects (12%) the presence of viral or Bb genome was also revealed.

Conclusions: The genome of cardiotropic infectious agent, viral or Bb, is present in the myocardium of more than half of the patients with new-onset unexplained DCM. Notably, Bb genome can be detected in almost one quarter of these subjects, which may have important therapeutic consequences. However, adenovirus infection does not seem to play an important role in the pathogenesis of new-onset unexplained DCM. Therefore, it is not necessary to perform adenovirus PCR assay of EMB specimens in patients with new-onset unexplained DCM.
Etenrecept treatment improves acute chagas disease and alters cardiac conduction and repolarization parameters

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Background: Chagas disease affects 8 million people in Latin America. Even some decrease in transmission has been achieved, recently acute cases especially by oral transmission has been reported. The Tumoral Necrosis Factor (TNF-α) plays a key role in the immune response against the Trypanosoma cruzi, but is not clear their beneficial or deleterious effects on disease outcome. In this sense, the aim of this work is to determine the effects of the TNF blocker etanrecept on inflammation parameters, ECG recordings and survival in an acute infection with a wild T. cruzi virulent strain.

Methods: NMRI male mice (30 g) were infected with 1000 trypomastigotes per gram and treated subcutaneously with 0.3% mg/kg at etanrecept 7 day post infection(dpi). Levels of TNF and C reactive protein (CRP) were determined in blood by semi-quantitative RT-PCR and ELISA respectively at day 0, 7, 14 and 21 dpi. Vertical, horizontal motility and mechanical allodynia were recorded with an automated activity cage and a dynamic plantar aesthesiometer during the last, and second week post-infection. ECG was taken weekly with surface electrodes coupled to a Bio amplifier.

Results: The survival of treated animals was increased significantly with respect to infected untreated animals (20 vs 24 days, p < 0.0048). The peak of CRP was at 7 dpi and decreased until 21 dpi in all groups, but the levels were significantly lower in treated animals. TNF relative levels peak occurred at 7dpi and there was no differences between treated and untreated animals. Vertical and Horizontal motility reduction and hyperalgesia in infected animals was reversed by etanrecept treatment. Finally, the infected animals showed Tawee height and repolarization slope reduction. However, was observed an alteration of ECG parameters that could be associated with arrhythmogenesis and progression to chronic cardiomyopathy, which suggest an role ofTNF-α in cardiac regional response.

Conclusions: Acute and viral myocarditis are characterized by elevated concentrations of hs-TNT. However, these biomarkers do not replace EMB for diagnosis of myocardial inflammation.

MYOCARDIAL INVOLVEMENT IN SYSTEMIC DISEASES

Measurement of interatrial dyssynchrony using tissue doppler imaging predicts functional capacity and cardiac involvement in systemic sclerosis


Background: Heart involvement in systemic sclerosis (SSc) is associated with poor prognosis, and early detection is crucial. SSc may affect all heart structures, including conduction pathways: interatrial block is considered common and may reflect atrial involvement, but has been so far poorly evaluated. Echocardiography may detect interatrial dysssynchrony, using either M-mode, Doppler or strain modality.

Methods of the study: 1) To assess the prevalence of interatrial dyssynchrony (IAD) by measuring the interatrial-electro-mechanical delay (IAMD) in SSc patients using TDI. 2) To evaluate the correlation between IAMD and other usual follow-up parameters.

Methods: Patients with SSc were selected if they were in sinus rhythm and were able to walk. The following data were collected: NYHA functional class and distance walked in 6 minutes (6'WD); P wave duration on ECG; serum creatinine and NT proBNP levels. Echo-Doppler study comprised: left ventricular (LV) mass, LV systolic and diastolic function, right ventricular (RV) function, pulmonary artery pressure (PAP), left atrial (LA) volumes and function. IAMD was assessed using colour TDI study, by measuring the delay between annular tricuspid and mitral a' waves. A cut off value of 35 ms was chosen to define the presence of IAD.

Results: Forty patients were studied. Forty% of patients were found to have IAD. These patients were significantly older. Using age-adjusted analysis, patients with IAD had more severe symptoms, lower 6'WD, higher NT proBNP and creatinine levels, and longer P wave duration than patients without IAD. No difference was found regarding LV dimension and LV EF. LV mass was higher, E/A and E'/E ratio were significantly different. LA volume was significantly higher, TAPSE was lower, and PAP was higher. Most importantly, IAMD correlated well with 6'WD (r = 0.72, p = 0.0001). During a follow-up of 5 patients died or had severe events: all of them were in the dysssynchrony group.

Discussion: The prevalence of interatrial dysssynchrony among SSc patients is high (40%). IAD was found to be associated with lower exercise capacities, altered LV diastolic function, decreased LA and RV function, increased pulmonary pressure, and increased natriuretic peptides. This finding suggests that IAD may represent a marker of myocardial involvement and may indicate a poorly compliant left atrium.

Conclusion: IAMD is a simple parameter showing good correlations with all other usual indices of heart involvement. We believe that it should be added to the routine echocardiography to evaluate patients with newly diagnosed SSc, and that its prognostic value should be evaluated.

Diagnosis and prognostic value of biomarkers in suspected myocarditis

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Background: Myocarditis can be associated with increased markers of myocardial injury. However, data on novel biomarkers as high-sensitive Troponin (hs-TnT) or Copeptin are lacking. The aim of this study was to determine the diagnostic and prognostic utility of biomarkers in patients with suspected myocarditis.

Methods: Seventy patients with suspected myocarditis (age 43.4±17.8 years, 76% male, male female ratio 36.9±17.8%, 76% in NYHA class III/IV) underwent a multimodal evaluation. In 44 patients, TNF-α was measured with PCR with primers (PCR assay). Details of the PCR assay are shown in Table 1. The ECG was performed daily during hospitalization. The following data were recorded: ECG, troponin I, Copeptin, NT proBNP and MR-proADM were analyzed. A ROC curve was constructed for each biomarker.

Results: According to EMB 6 patients were diagnosed with acute myocarditis (AM) and 36 patients with chronic myocarditis (CM). In 28 patients, EMB revealed no myocardial inflammation (NM). Acute myocarditis was associated with high levels of TNF-α, Copeptin, NT proBNP and MR-proADM, no significant differences existed between the groups. The concentration of hs-TNT was significantly higher in viral myocarditis compared to non-viral myocarditis (37.4±19.6 pg/ml versus 15.0±10.4 pg/ml, p<0.005). During the last week of the study, patients with AM had higher NT proBNP in the highest quartile >4225 ng/ml) was predictive for cardiac death or heart transplantation (hazard ratio 9.2; 95% confidence interval 1.7-50; p=0.011).

Conclusions: Myocardial mechanics for the early detection of cardiac sarcoidosis

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Purpose: Speckle tracking has emerged as valuable tool for a more comprehensive assessment of regional myocardial function, providing angle-independent measurements of strain. The aim of this study was to evaluate left ventricular (LV) function in patients with newly diagnosed sarcoidosis, utilizing the novel method of 2D speckle tracking.

Methods: 67 patients with newly-diagnosed sarcoidosis and with unremarkable medical history of cardiovascular disease, as well as 29 healthy age- and gender-matched controls underwent echocardiographic study. Apical 4-, 2-, 3-chamber as well as short axis acquisitions were made. In addition to conventional 2D, Doppler and TDI measurements, speckle tracking echocardiography was applied and LV global longitudinal strain was derived from the obtained images. Moreover, LV base and apex rotation angles were assessed from which LV twist was derived.

Results: The mean age of patients (26 men) was 43±6.1 years old. Compared with controls, patients had similar conventional 2D and Doppler measurements. TDI revealed increased E/E' in the patient group vs control group (8.9±1.45 vs 4.7±1.29, p<0.05). Strain analysis demonstrated reduced global longitudinal strain values in the patient vs control group (18.98±1.89% vs 22.93±2.28%, p<0.05). Furthermore, twist was increased in the patient group as compared to the healthy individuals (13.1±2.3° vs 10.7±1.0°, p<0.05).

Conclusions: Speckle tracking echocardiography revealed alterations in strain and rotational indices, implying elevated filling pressures of the left ventricle. This could represent an early sign of myocardial involvement in patients with newly-
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Background: Growth hormone deficiency (GHD) is associated with increased cardiovascular events. We showed previously that adults with GHD have subclinical left ventricular (LV) longitudinal dysfunction; however, the right ventricular (RV) function was not assessed in these patients yet. Therefore, we evaluated RV function in GHD, by comparison with normal (N) subjects, and assessed if there is a relation between LV and RV dysfunctions.

Methods: 31 GHD patients (48±15 yrs, 20 males), free of any cardiovascular disease, were compared with 31 N, age- and sex-matched, using conventional echo and tissue Doppler. RV diameter (RVD), RV end-systolic, and end-diastolic indexed area (RVIDs, RVIDd) were assessed. Global RV function was evaluated from TAPSE, RV fractional area (RVFA), tricuspid inflow, isovolumic con- traction and relaxation times (TICV, TRIV), and TEI index; longitudinal RV systolic function from longitudinal systolic velocity (RVLVS), longitudinal strain (RVLSS) and strain rate (RVLSRs); longitudinal diastolic LV function from increased longitudinal systolic (LVLVE) and early diastolic strain rate (LVLVSRs).

Results: GHD patients had increased RVD and RVIDd, and lower TAPSE (Is-20±17, p<0.001 vs N-26±12), moderate, all RV longitudinal Doppler parameters were decreased (RVLVS, RVLSS, RVLSRs), with lower RVIDs and RVIDd. RVFA, E, A, TDE, TCV, TRIV, and TEI index were similar between groups. In GHD patients, RVLS correlated positively with LVLS (r=0.37, p<0.04), RVLSS and RVLSRs with LVLS, and RVLSS with LVFA and LVSS (r=0.46, r=0.40, both p<0.05).

Comparison between GHD and N

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GHD</th>
<th>N</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVD</td>
<td>43.6±5.3</td>
<td>35.0±3.2</td>
<td>0.003</td>
</tr>
<tr>
<td>RVIDd</td>
<td>113.2±23.8</td>
<td>120±28.9</td>
<td>0.030</td>
</tr>
<tr>
<td>RVIDs</td>
<td>28.8±9.1</td>
<td>28.9±10.0</td>
<td>0.919</td>
</tr>
<tr>
<td>TAPSE</td>
<td>6.1±1.7</td>
<td>6.6±1.9</td>
<td>0.003</td>
</tr>
<tr>
<td>RVLVS</td>
<td>-25.9±6.4</td>
<td>-28.9±7.2</td>
<td>0.009</td>
</tr>
<tr>
<td>RVLSS</td>
<td>-15.9±4.6</td>
<td>-16.1±5.1</td>
<td>0.001</td>
</tr>
<tr>
<td>RVLRSS</td>
<td>-5.9±2.6</td>
<td>-6.1±2.8</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusion: Patients with GHD have subclinical LV systolic and diastolic dysfunction, related to the concomitant LV longitudinal dysfunction. Our findings add supplementary arguments that GHD adults have intrinsic biventricular subclinical myocardial disease.

P4897 Impaired vascular elasticity and diastolic dysfunction in pseudoxanthoma elasticum

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Purpose: Pseudoxanthoma elasticum (PXE) is an autosomal recessive connec- tive tissue disease with involvement of the retina and the skin. It is caused by mutations in the ABCC6 gene, which encodes for a protein of the transmembrane protein superfamily involved in intracellular calcium homeostasis in the skin caused by decreased activity of the ABCG5/ABCG8 transporters. PXE is characterized by arterial and cardiac involvement, consisting of intimal thickening of the arterial wall, arterial calcification and aortic root abnormalities. Cardiac involvement is common and aortic root abnormalities have been observed in the endo-, myo- and pericardium and in the intima and media layers of medium sized blood vessels. Though cardiovascular involvement has been suggested in heterozygous carriers, controversy exists on the characteristics and relevance. We conducted an echocardiographic and vascular imaging study to determine whether these lesions influence ventricular function and the elastic properties of the middle-sized arteries in PXE patients and carriers.

Methods: 35 PXE patients, 22 carriers and 28 matched healthy subjects, aged between 18 and 70 years, were enrolled in this study. Measurements of global and local arterial stiffness (Pulse Wave Velocity (PWV) and carotid distensibility, and wave reflection (PWV); arterial stiffness and wave reflection (PWV)) were performed.

Results: The left ventricular diastolic dysfunction was impaired in PXE patients and carriers, with a significantly higher deceleration time (188±36.5 vs. 192.4±34.3, 138±36.5 vs. 135.6±0.01, p<0.001, respectively), significantly lower lower Em (9.5±2.7 vs. 9.9±2.6, 11.7±3.2; p<0.01, p<0.025, respectively) and significantly higher E/Em ratio (4.9±2.6; 8.4±1.8; 7.3±1.5; p<0.001, 0.04, respectively) in both patients and carriers when compared to the control group. PXE patients older than 35 years had a significantly higher PWV (8.5±2.7 versus 6.6±1.8; p<0.04). This observation was independent of the presence of cardiovascular risk factors, as determined by multiple logistic regression analysis. In the carriers we found a non signifi- cant increase in PWV. The distensibility of the middle sized arteries did not differ between groups. The Intima Media Thickness was significantly higher in both patients and carriers versus healthy controls (0.50±0.13 ± 0.51±0.01 mm, 0.11±0.42mm±0.1; p<0.004, 0.01, respectively).

Conclusions: The results of this study clearly indicate the presence of left ventricu- lar diastolic dysfunction as well as impaired elastic properties of middle-sized
arteries in PXE patients independently of the presence of cardiovascular risk factors. In heterogeneous carriers, diastolic ventricular function is also abnormal, indicating cardiovascular involvement and the need for cardiovascular assessment in this specific group.

### P4989 Differential effect of antiretroviral drug regimens on aortic elastic properties in HIV infected individuals

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**Purpose:** Aortic elastic properties mediate cardiovascular performance. Pulse wave velocity (PWV), an index of aortic stiffness, is an independent predictor of future outcomes. HIV infection is linked to higher cardiovascular risk and certain classes of antiretroviral therapy (ART) drugs, i.e. protease inhibitors, increase this risk disproportionately. The aim of the study was to assess the interplay of ART and arterial stiffness. Moreover, we sought to investigate how different ART regimens are linked to arterial stiffness.

**Methods:** 51 HIV infected patients were studied (50 men, age 40±10 y.o.). 12 were naïve to treatment, 39 were on ART. Among the ART treated, 22 were on a combination of nucleoside reverse transcriptase inhibitors plus non-nucleoside reverse transcriptase inhibitor (NNRTI) and 17 were on a combination of nucleoside reverse transcriptase inhibitor plus protease inhibitor (PI). Carotid-femoral PWV was measured non-invasively with a validated device (Complior).

**Results:** Naïve patients had lower values of PWV compared to patients on ART (7.45 vs. 7.74 m/sec, P=0.05). Regarding drug regimens, those on NRTI/PIs had higher levels of PWV compared to those on NRTI/NNRTIs and to naïve to treatment patients (7.98±1.83 m/sec vs 7.04±1.21 m/sec vs 6.68±0.98 m/sec respectively, P=0.037 for overall ANOVA) (Figure).

**Conclusions:** HIV patients on ART have higher levels of aortic stiffness compared to naïve patients. Moreover, NRTI/PIs leads to heightened levels of PWV compared to NRTI/NNRTIs. These findings suggest that the detrimental effect of PIs on cardiovascular outcomes may be mediated through mechanisms of aortic dysfunction. Measurements of aortic stiffness in the setting of HIV infection can aid in risk stratification.

### P4999 Study of heart involvement in Kawasaki disease: a multicenter study

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**Introduction:** Kawasaki disease happens mostly in children less than 5 years of age and presents itself as an acute and self-limiting disease with worldwide spread. One of the important aspects of this disease is the serious heart mortality it can cause if undetected. Coronary vessels are the most common site of heart involvement. The aim of this study was to determine demographic of heart findings in Kawasaki patients. We also studied age and sex and their relation with heart findings in patients suffering from Kawasaki disease.

**Methods:** A prospective study of patients suffering from Kawasaki disease in two hospitals from year 2000 to year 2005 was performed. Findings: 97 patient had Kawasaki disease 65 (66.9%) were male and 32 (33.1%) were female, 75 (77.3%) were below five years of age and 22 (22.7%) above. 32 (32.9%) had one or more heart involvement. From patients with heart involvement 20 (62.5%) were male and 12 (37.5%) were female. 22 (67.7%) of patients with heart involvement were under 5 years of age and 7 (12.8%) were from 6 to 10 years old and 3 (9.3%) over 10 years old. The highest age among patients was 11/5 years. The distribution of heart involvement was 23 (23%) pericardial effusion (the highest heart involvement), Coronor dilatation and Aortic stenosis with each 2% patients were the rarest heart findings.

**Conclusion:** In this study we assessed the RV remodeling with 3DE and CMR during a follow up of 2 years and we associated RV volumetry with clinical deterioration. Further investigation is needed to find out whether this improvement is secondary to a functional recovery of the RV or to a decrease in RV afterload. We suggest routine measurement of RV S to follow up the disease progression.

### P4990 PULMONARY HYPERTENSION IMAGING


In patients with pulmonary hypertension (PH), progression of the disease and survival are related to the capability of the right ventricle (RV) to adapt to the chronically elevated pulmonary artery pressure (sPAP). Recent studies have successfully applied speckle-tracking derived strain (S) to quantify RV dysfunction in PH. Little is known about RV deformation evolution under pulmonary vasodilator (PV) treatment.

**Methods:** We performed echocardiographic follow-up of 17 patients with PH (Groups I and IV of the Dana Point classification) during 13.2±5.8 months and measured RV longitudinal systolic S from 6 RV segments. All cases were under PV treatment according to their physician’s criteria.

**Results:** We found a significant improvement in most conventional echocardiographic measurements as well as global and regional S during follow-up (table 1, figure 1).

**Table 1. Echocardiographic parameters evolution during follow-up**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>12 months</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAC (%)</td>
<td>28.3</td>
<td>32.1</td>
<td>0.05</td>
</tr>
<tr>
<td>TAPSE mm</td>
<td>27.8</td>
<td>29.5</td>
<td>0.05</td>
</tr>
<tr>
<td>sPAP mm Hg</td>
<td>210.3</td>
<td>130.2</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Conclusion:** RV performance as measured by S significantly improves during follow-up in PH patients who are under PV treatment. Further investigation is needed to find out whether this improvement is secondary to a functional recovery of the RV or to a decrease in RV afterload. We suggest routine measurement of RV S to follow up the disease progression.
Echocardiographic prognostic factors for mortality in pulmonary hypertension: way beyond tricuspid annular displacement


Right ventricular (RV) function is the main determinant of morbidity and mortality in pulmonary hypertension (PH), and echo-derived tricuspid annular plane systolic excursion (TAPSE) has a well-recognized prognostic importance in this setting. Recently, RV deformation parameters have shown to accurately quantify RV function in PH. The aim of our study was to find out whether RV-spectre-derived strain (S) may have an additional prognostic role for PH patients when added to classic RV function measurements such as TAPSE.

Methods: We prospectively studied 55 patients with PH of varied etiology and 22 controls. RV longitudinal systolic S was evaluated by echocardiography for 6 RV segments (from the 4-chamber apical view). Results: We found a significant reduction of global and regional S in PH patients when compared to controls (15.5±5.9 vs. -25.9±3.9, p<0.005). During a mean follow-up of 9.2±7.1 months, 8 cardiovascular (CV) events (death and cardiac or pulmonary transplant) occurred. We identified two variables significantly associated with CV events: TAPSE (p=0.005) and S (p=0.002). Global S was found to improve the Area Under the ROC Curve (AUC) for the prediction of adverse CV events when added to TAPSE (from 0.841 (P<0.05) to 0.907 (P<0.05), figure 1a). Kaplan-Meier survival analysis showed that the subgroup of patients with low TAPSE and low S had a marked predisposition to clinical deterioration and death when compared to the groups with either low TAPSE or low S alone (figure 1b).

Conclusion: In our study global S has shown an additional value for the prediction of CV events when added to TAPSE. Therefore we suggest the routine assessment of deformation parameters for the follow-up of PH patients.

Echocardiography of pulmonary vascular function in asymptomatic carriers of the bone morphogenetic protein receptor type 2 mutation

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Purpose: Relatives of patients with idiopathic pulmonary arterial hypertension (IPAH) tend to present with enhanced pulmonary vascular responses to exercise or hypoxia as measured by the maximum velocity of tricuspid regurgitation (TRV), this may be driven by carriers of a mutation of the bone morphogenetic protein receptor type 2 (BMPR-2). We wondered if this potentially important risk factor might better defined by more extensive study of pulmonary vascular function.

Methods: Echocardiographic measurements were performed during an incremental exercise test and during 2 hours of hypoxic breathing in 35 relatives (of whom 5 were carriers of a BMPR-2 gene mutation) of IPAH patients, and in 38 healthy controls. Pulmonary artery pressures (PAP) were estimated from TRV, total pulmonary vascular resistance (PVR) was calculated from the right ventricular outflow-time velocity integral and TRV, and cardiac output (Q) from left ventricular outflow tract velocity. Multipoint PAP-Q relationships and a distensibility coefficient, alpha were also derived.

Results: In BMPR-2 carriers, non carrier relatives and controls, PAP at an average workload of 100 watts and after 120 min of hypoxia, and the PAP-Q slopes were not different. However, alpha was markedly decreased in BMPR-2 carriers, at rest (0.018±0.005 vs 0.034±0.004 vs 0.029±0.004/mmHg, p<0.05) and exercise (0.012±0.004 vs 0.021±0.002 vs 0.015±0.009/mmHg, p<0.05). The hypoxia induced increase in PVR was greater in the relatives with BMPR-2 compared to relatives without mutations.

Survival in pre-capillary pulmonary hypertension: does echocardiography make the difference?


Purpose: The aim of this study was to assess pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) patients' survival in relation to a prospective, protocol-based collection of echocardiographic data in pre-capillary pulmonary hypertensive patients, referred to the National Pulmonary Hypertension Centre in London. All patients received the guideline-induced best medical therapy.

Methods: All patients referred to the National Pulmonary Hypertension Service from 2002 until 2010 were included in the study. The patient cohort was solely focused in all pre-capillary pulmonary hypertensive patients and consisted of 777 consecutive patients. The data was analysed using a univariate and multivariable time-dependent Cox model. The survival outcome was determined by death. Of 777 patients, 195 (25.1%) died. Median follow up of patients was 4.7±5.2 years. Echocardiographic indices were inserted into univariate and multivariable analysis according to the cause (pulmonary arterial hypertension vs. chronic thromboembolic pulmonary hypertension) and Youden cut-off values were used for the overall population as well as for the establishment of a prognostic index. Heagerty time-dependent ROC curves were employed for the predictive value of each parameter.

Results: The overall survival was best determined by the severity of tricuspid regurgitation (p=0.001, HR=10.98), the presence of pericardial effusion (p=0.0003, HR=1.714) and the composite score of RV systolic function (p=0.0002, HR=1.37), followed by left atrial diameter (p=0.0349, HR=1.04), the diameter of inferior vena cava (p=0.001, HR=0.896) and the echocardiographic measurement of pulmonary vascular resistance (p=0.0002, HR=0.822) that were the strongest predictors of mortality.

A greater than moderate tricuspid regurgitation, pericardial effusion, a greater than moderate impaired RV systolic function, pulmonary end-diastolic pressure more than 20.9 mmHg, a diameter of inferior vena cava ≥ 21.8 mm, a pulmonary vascular resistance ≥ 8.9 Wood units and a RV cardiac output < 3.45 l/min, on initial echocardiographic assessment indicate a poor survival.

Conclusion: In a large group of consecutive pre-capillary pulmonary hypertensive patients, the severity of tricuspid regurgitation, RV systolic function and the presence of pericardial effusion may indicate poor survival. Inoperable CTEPH patients had worse survival when compared to patients with pulmonary arterial hypertension.
Improving echocardiography estimation of right atrial pressure: comparison among several models and a new one based on right atrial evaluation

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Purpose: The estimation of right atrial pressure (RAP) has a great impact on the non-invasive evaluation of pulmonary hemodynamics. Several models have been developed to estimate RAP based on the inferior vena cava (IVC) diameter and collapsibility. However, IVC evaluation is not reliable for intermediate RAP values, young athletes, patients on ventilators or bad subcostal window.

The aim of this study was to compare several known models of RAP estimation against the invasive RAP (iRAP) and develop a new one to overcome the limitations of IVC analysis.

Methods: Echocardiography was performed on 75 patients within 60 minutes from cardiac catheterization. IVC was evaluated in long and short-axis view. Images of right chambers, tricuspid Pulsed and Tissue Doppler, and hepatic vein flow were acquired. RAP was estimated using 5 different known models based on IVC evaluation and a new one based on right atrium analysis.

All RAP models were compared to iRAP by Bland-Altman analysis.

Results: A population of 75 patients was evaluated (age: 62±14 years; iRAP: 9.5±2.2 mmHg [7-12]; range 1 - 22 mmHg). IVC measured by Mnmode in long-axis view showed better correlation with iRAP. Among the 5 models based on IVC, the most recent one performed better (r = 0.29; p=0.04), but had a wide confidence interval (13.3, 0.1 11.6 mmHg). Right atrial total ejection fraction (ToEF) and systolic volume (sVol) showed a strong positive (sVol) and inverse (ToEF) linear association with iRAP (r=0.0001). Our model based on these parameters performed significantly better (r=0.48; p<0.001) and had a narrower confidence interval (-8.9, +8.4 mmHg) (see figure).

Conclusion: Echocardiography can provide a better estimation of RAP helping to improve non-invasive pulmonary pressure estimations.

Figure 1. Comparison of RAP models

Conclusions: The adoption of a new model based on RA morphology and function can provide a better estimation of RAP helping to improve non-invasive pulmonary pressure estimations.

An echocardiographic score for evaluating the pre-test probability of having a pre-capillary rather than a post-capillary pulmonary hypertension

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Aim: To provide an easy and integrated echo-score for evaluating the pre-test probability of having a pre-capillary (pre-PH) rather than post-capillary (post-PH) pulmonary hypertension (PH).

Methods: One hundred thirty-five consecutive patients referred to our PH center from January to December 2011 underwent standard Doppler echocardiography (DE) within 1 hour of a clinically indicated right heart catheterization (RHC). The DE was scored on the basis of features suggesting pre-PH: right atrium (RA) > left atrium (LA), right ventricle (RV) > left ventricle (LV), apex forming RV, LV eccentricity index (EI) > 0.3, pericardial effusion (PE), systolic notch at right ventricular outflow tract (RVOT) pulsed wave Doppler, dilated and fixed inferior cava vein (ICV) (score for yes = 1, no = 0), or post-PH: LV ejection fraction (EF) <40%, moderate to severe aortic and/or mitral disease (score for yes = 1, no = 0). The echo score ranged from -2 to 7. Patients were arbitrarily divided in 3 groups: low score (-2 to 0), medium score (1 to 2) and high score (3 to 7) probability of having pre-capillary PH.

Results: Twelve/135 patients did not have pulmonary hypertension at RHC, 84 patients showed pre-capillary PH (54 group 1, 22 group 3 and 8 group 4) and 39 post-capillary PH (group 2) at RHC. The probability of having pre-PH was 37% in presence of low, 66% in presence of medium and 95% in presence of high echo-score (0.9). No patient with LV-EF <40% had pre-PH (specificity for post-PH = 100%). The majority of echo features showed an high specificity but a low sensitivity for pre-capillary PH (table).

Echo features for pre-capillary PH

<table>
<thead>
<tr>
<th>RA/LV</th>
<th>RV/LV</th>
<th>Apex RV</th>
<th>RV EI &gt; 0.3</th>
<th>LV EI</th>
<th>PE</th>
<th>RVOT notch</th>
<th>Diastolic fixed LV</th>
<th>LV EF &gt; 40%</th>
<th>Left valve flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>48</td>
<td>52</td>
<td>56</td>
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<td>35</td>
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<td>96</td>
<td>81</td>
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<tr>
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<td>12.9</td>
<td>15.1</td>
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<td>13.2</td>
<td>1.2</td>
<td>3.2</td>
<td>0</td>
<td>6.4</td>
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| RV = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle; EI = eccentricity index; PE = pericardial effusion; RVOT = right ventricular outflow tract; ICV = inferior cava vein; LV EF = left ventricular ejection fraction.

Conclusion: Echocardiography can provide a better estimation of RAP helping to improve non-invasive pulmonary pressure estimations.

Pulmonary artery trunk dilation in symptomatic subjects referred for coronary artery calcium scoring by means of a 64-slice cardiac computed tomography

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Non-contrast cardiac computed tomography is as established method for coronary artery calcium determination in both symptomatic and asymptomatic subjects. We aimed at assessment of the prevalence of ancillary findings, including pulmonary artery dilation.

1075 females and 484 males examined between March 2010 and January 2012 were examined for CAC scoring by means of cardiac MDCT (64-slice Aquilion). A retrospective analysis of the data for evaluation of pulmonary artery trunk diameter (PAD, mm) was performed. Gender-dependent upper normal limits were established in 74 women and 50 men with normal CT scanning, zero CAC score, who were never smokers, non-obese, non-diabetic and non-hypertensive. Proportion of subjects with abnormal PAD was determined separately in men and women.

Abnormal PAD was detected in 209 women (19%), while increased PAD:AAD ratio in 57 women (5%). In total, the PA dilation was found in 219 women (20.3%) including 172 with one measure abnormal, and 47 with both measures abnormal. Among men, abnormal PAD was detected in 89 subjects (18%), while abnormal PAD:AAD ratio in 9 men (2%). In total, any PAD increase was found in 82 men (17%) and both measure abnormal was found in 8 subjects (2%). Logistic regression analysis revealed that independent predictors of PAD increase in females were a positive CACS (OR 2.78) and obesity (1.83). Similar determinants were recognized in men (a positive CAC OR 2.04) and obesity (OR 1.36).

Conclusions: Pulmonary artery trunk dilation is relatively frequently observed in subjects referred for coronary artery calcium determination. Presence of coronary atherosclerosis and obesity were found as independent predictors of PAD enlargement. Detection of PAD abnormality might help to optimize diagnostic and therapeutic approaches in symptomatic subjects referred for CAC scoring.

Pulmonary vasculopathy assessed by intravascular ultrasound in patients with severe chronic respiratory failure evaluated for lung transplantation:
comparison to pulmonary arterial hypertension


Purpose: The aim of the study is to assess pulmonary vasculopathy (wall fibrosis, pulmonary arterial pulsatility and elastic modulus) in patients with chronic respiratory failure evaluated for lung transplantation, by means of intravascular ultrasound (IVUS) in medium sized pulmonary arteries, and to compare it to pulmonary arterial hypertension (PAH) and healthy controls.

Methods: We studied 37 patients, 9 Group 1 (pre-lung transplantation, COPD, pulmonary fibrosis, NYHA 3-4), 18 Group 2 (PAH, NYHA 2-3) and 10 in Group 3 (healthy controls). Group 1: 2 females, 59±8 years. Group 2: 14 females, 53±14 years and Group 3: 6 females, 51±5 years.

All patients were submitted to left and right heart catheterization, and IVUS in medium sized elastic PA (2-3 mm diameter) of the inferior lobes.
Egr-1 expression is specific for neointimal development. This suggests that Egr-1 is an important regulator in the development of non-neointimal PH. Egr-1 is upregulated and associated with neointimal development in both human and experimental PAH. In Pulmonary Arterial Hypertension (PAH) due to congenital heart disease, increased pulmonary blood flow is an essential trigger for neointimal formation. Using micro-array analysis, we recently identified that transcription factor Egr-1 is upregulated in experimental flow-associated end-stage PAH. Its role in neointimal development in PAH is unknown.

Here, we aimed to assess in both human and rats spatiotemporal expression of Egr-1 in neointimal (flow-associated) PAH compared to non-neointimal Pulmonary Hypertension (PH).

**Methods:** In rats, flow-associated PAH was created by combining monocrotaline with an aortocaval shunt (MCT+Flow); and compared with a non-neointimal PH model (MCT-only). Animals were sacrificed 1 day before increased flow and at multiple time points after flow addition (1 day, 1 week, 4 weeks). Egr-1 expression was assessed immunohistochemically in lung samples of 27 PAH patients (associated with congenital shunt) (flow PAH, n=12; IPAH, n=15) and compared with non-neointimal PH (hypoxia PH; n=10) and healthy controls (n=11).

**Results:** In rats, MCT+Flow rats developed within 4-5 weeks, severe PAH (P<0.05 vs IPAH; P<0.001), and controls (P<0.001). Egr-1 expression was observed only sporadically in the non-neointimal vessel remodeling. In both flow PAH and IPAH patients, Egr-1 expression was upregulated compared to hypoxic PH (P<0.001) and controls (P<0.001). The strongest expression was seen in the in-situ carina of vessels of flow-PH (P<0.005 vs IPAH; P<0.001 vs hypoxic PH and control) and in plevis flows. In flow-PH, endothelial Egr-1 expression in the in-situ carina vessels correlated with increase in pulmonary artery pressure (mmHg).

Conclusions: We show that in both experimental human and PAH, but not in non-neointimal PH, Egr-1 is upregulated and associated with neointimal development. This suggests that Egr-1 is an important regulator in the development of pulmonary neointimal lesions in PAH.
mainly incompletely understood. Besides the increase in afterload, inflammation and oxidative stress have been identified as important cofounders for induction of right heart dilatation and failure. Nitrated fatty acids (NO2-FA) represent endogenously generated biomolecules, which convey potent anti-inflammatory and anti-oxidative effects. We have shown recently that these molecules are strongly cardioprotective. Whether NO2-FA modulate the development of right heart failure in PAH however remains unknown.

**Methods and Results:** Wild-type C57BL/6J mice were housed under hypoxic conditions (10% oxygen concentration) and treated for 4 weeks with vehicle or nitro-oleic acid (OA-NO2, 6 mg/kg bodyweight, n=8) via subcutaneous minipumps. Animals treated with OA-NO2 displayed a reduced right ventricular pressure as assessed by in vivo-right heart catheterization (RVP = 48.67±2.05 vs. 54.0±1.30 mmHg, p<0.01) and relative right ventricular hypertrophy (RVLV weight 0.25±0.01 vs. 0.37±0.02 sec, p<0.01) as compared to vehicle-treated animals. This translated in significantly reduced right heart failure as determined by BNP (p<0.05). Leukocyte infiltration as well as oxidative stress superoxide bioavailability in the right ventricle were significantly reduced following OA-NO2 treatment. In addition, microcircus red staining revealed attenuated ventricular fibrosis in response to OA-NO2 (1.22±0.05 vs. 2.05±0.43 vs. 2.33±0.31 in vehicle treated animals, p<0.05).

**Conclusions:** The current findings not only underscore the significance of inflammation and oxidative stress in the pathophysiology of right ventricular dysfunction in pulmonary hypertension, but reveal that nitrated fatty acids may provide a novel therapeutic option in pulmonary arterial hypertension.

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**P4914**

**New single nucleotide polymorphisms associated with altered platelet response to acetylsalicylic acid in diabetic population: genome-wide association approach and pooled DNA strategy**

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**Purpose:** To investigate whether hypercholesterolemia and failure of the right ventricle changes the response to ischemia and ischemic preconditioning.

**Materials and Methods:** Male Wistar rats were subjected to moderate pulmonary trunk banding (mPTB), severe PTB (sPTB) or SHAM operation. The degree of right ventricular hypertrophy and failure (RVHF) where evaluated by right ventricular mass, echocardiography of the right heart and clinical signs of heart failure. Four weeks after the operation, hearts were isolated and perfused a.m. *Langendorff* with Krebs-Henseleit buffer. They were randomised to either IPC (2 x 5 min ischemia/10 min reperfusion), or controls (CON). IPC did not improve IS/AAR or hemodynamic recovery (fig. 1).

**Results:** Right ventricular hypertrophy and failure abolish cardioprotection by ischemic preconditioning

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**Purpose:** To investigate whether hypertrophy and failure of the right ventricle changes the response to ischemia and ischemic preconditioning.

**Materials and Methods:** Male Wistar rats were subjected to moderate pulmonary trunk banding (mPTB), severe PTB (sPTB) or SHAM operation. The degree of right ventricular hypertrophy and failure (RVHF) where evaluated by right ventricular mass, echocardiography of the right heart and clinical signs of heart failure. Four weeks after the operation, hearts were isolated and perfused a.m. *Langendorff* with Krebs-Henseleit buffer. They were randomised to either IPC (2 x 5 min ischemia/10 min reperfusion), or controls (CON). IPC did not improve IS/AAR or hemodynamic recovery (fig. 1).

**Results:** The mPTB procedure caused compensated RV hypertrophy and the sPTB caused RV hypertrophy with failure compared to SHAM. Hypertrophy of the RV caused an increase in infarct size in hearts from mPTB and sPTB animals compared to SHAM (fig. 1). Cardioprotection by IPC was possible in SHAM and mPTB hearts measured by a decrease in IS/AAR and improved hemodynamic recovery of RV contractile function. In sPTB hearts with hypertrophy and failure IPC did not improve IS/AAR or hemodynamic recovery (fig. 1).

**Conclusion:** Right ventricular hypertrophy increases infarct size, and when failure is present, abolishes cardioprotection by ischemic preconditioning in the right ventricular myocardium of the rat.
1.477 (95% CI 1.06-2.05) and 0.476 (95% CI 0.29-0.75) and 0.451 (95% CI 1.11-2.40) × 0.043 × (age years) + 0.0169 × body mass (kg). The algorithm was tested on a validation group of 33 patients. The accuracy of dose calculation was 66.6%. The algorithm will be evaluated on a larger group of patients.

Conclusions: Prevalence of VKORC1 and CYP2C9 polymorphisms in Polish population is similar to that of other Caucasians. Genotype, age and body mass are independent determinants of dose requirements for Acenocoumarol.

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**P4918** Association between a genetic variant near adrenomedullin gene with left ventricular mass index

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Purpose: Adrenomedullin (ADM), is a multifunction peptide that has been reported to prevent myocardial and fibroblastic hypertrophy. Its plasma concentrations are correlated to cardiovascular risk factors and hemodynamic compromises. We assessed the relationship between genome-wide association study-identified variants associated with MRproADM levels and left ventricular mass index (LVM).

Methods: LVM was measured upon ASE recommendations on 4 axis view from the apical window in a population of 5000 European-ancestry adults from the Gutenberg Health Study Cohort. Biometric, Clinical and biological variables, as well as genetic markers identified by a genome-wide association study (Affymetrix SNP array 6.0) were analyzed to identify correlates of LVM. The models were corrected for multiple testing.

Results: rs2957692 (p=1.54 x 10-13) and rs2957717 (p=2.4 x 10-8), located 39Kb and 53Kb upstream the ADM gene were previously identified as independent correlates of MRproADM plasma levels. The minor allele of rs2957717 (T) was associated with a decrease in ADM levels as well as lower left ventricular mass index on univariate analysis (figure). After adjustment on age, gender, smoking, hypertension, diabetes, hyperlipidemia as well as plasma levels of MRproADM, such relationship still remained significant (Bonferroni’s p=0.04).

Conclusions: The variant rs2957717, near the ADM gene, was associated with both lower levels of MRproADM and left ventricular mass index in the general population. The effect on left ventricular mass index was independent of MRproADM levels and cardiovascular risk factors. Such finding supports the hypothesis of a possible causal relationship between the variant and left ventricular mass warranting further investigation.

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**P4917** Influence of genetic polymorphisms of alpha-adrenergic receptors, endothelial nitric oxide synthase and bradykinin receptor B2 on treadmill exercise test responses

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Purpose: Treadmill exercise testing responses have been associated with cardiovascular prognosis in individuals without overt heart disease. Neurohumoral and nitric oxide responses may influence cardiovascular performance during exercise. The aim of this study was to evaluate associations between genetic polymorphisms of alpha-adrenergic receptors (ADRA1A, ADRA2A and ADRA2B), endothelial nitric oxide synthase (eNOS) and bradykinin receptor B2 (BKGR) and treadmill exercise test responses in individuals without overt heart disease.

Method: We enrolled 766 (417 women and 349 men) asymptomatic subjects. We selected the following variables during a maximal symptom-limited treadmill exercise test: exercise capacity, chronotropic reserve, maximum heart-rate achieved, heart-rate recovery, exercise systolic blood pressure, exercise diastolic blood pressure and systolic blood pressure recovery. Genotypes for the ADRA1A Arg347Cys (rs1048101), ADRA2A C1780T (rs556668), ADRA2B Del 301-303 (rs2865503), eNOS T786C (rs207044), eNOS GIIu298Asp (rs1799883) and BKGR B5810761 polymorphisms were assessed by polymerase chain reaction (PCR) followed by restriction enzyme digestion. Genotyping data were collected for all participants. Statistical analysis was performed with multiple regression models for women and men.

Results: The genotype frequencies were under Hardy-Weinberg equilibrium, except for the ADRA2B Del301-303 polymorphism. In the multivariated analysis the ADRA2A C1780T polymorphism was significantly associated with exercise diastolic blood pressure in both sexes. Exercise diastolic blood pressure was higher in individuals with TT genotype than in C allele carriers (P=0.003 for women; P=0.007 for men) (Table 1). The other polymorphisms did not influence significantly the treadmill exercise test responses.

Conclusions: The ADRA2A C1780T influenced the exercise diastolic blood pressure in both sexes. This finding suggests that this polymorphism may be a marker of blood pressure response during exercise.

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**P4916** Low-frequency intermediate penetrance variants in the ROCK1 gene predispose to congenital heart disease

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Background: Epidemiological studies indicate a substantial excess familial recurrence of non-syndromic Tetralogy of Fallot (TOF), implicating genetic factors that remain largely unknown. The Rhö inducible kinase 1 gene (ROCK1) is a key component of the planar cell polarity signaling pathway, which plays an important role in normal cardiac development. The aim of this study was to investigate the role of genetic variation in ROCK1 on the risk of TOF.

Methods: ROCK1 was sequenced in a discovery cohort of 93 non-syndromic TOF probands to identify rare variants. TagSNPs were selected to capture common variation in ROCK1. Novel variants and TagSNPs were genotyped in 458 TOF cases and 1920 healthy controls.

Results: A novel rare SNP (c.807C>T) was associated with TOF risk (OR 4.29 [95% CI 1.91-9.60]; p=0.0004). The minor allele frequency of c.807C>T in the controls was 0.003, and the variant accounted for 2% of the population attributable risk (PAR) of TOF. There was also significant association with TOF for an uncommon SNP in ROCK1, rs2889799 (OR 1.94 [95% CI 1.59-2.39]; p=1.9x10-5). The minor allele frequency of rs2889799 in the controls was 0.043, and the variant accounted for 11% of the PAR of TOF. These association signals were independent of each other.

Conclusions: We conclude that low frequency intermediate penetrance (LFIP) variants in the ROCK1 gene predispose to the risk of TOF.

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**P4919** Systematic testing of literature reported genetic variation associated with restenosis after percutaneous coronary intervention: results of the genetic determinants of restenosis study

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Purpose: Despite all medical advances, coronary restenosis after percutaneous coronary intervention still is a significant problem. Unraveling the mechanisms leading to restenosis development remains challenging. Although many studies have identified genetic markers associated with restenosis, consistent replication of the reported markers is scarce, mainly due to small sample sizes, heterogeneity of the phenotype and lack of proper replication cohorts. The aim of the current study was to analyze the joined effect of previously in literature reported candidate genes for restenosis using the gene-set analysis of GENetic DEterminants of Restenosis (GENDER) database.

Methods: Candidate genes were selected using a search on MEDLINE including the terms ‘genetic polymorphism’ and ‘coronary restenosis’. The final set included 36 genes. All single nucleotide polymorphisms in the genomic region of each gene, including a 10Kb window, were analyzed using set-based analysis in PLINK in the GENDER database, containing genotypic data of 2,575,000 SNPs of 295 patients who developed restenosis (cases) and 571 matched controls.

Results: The set including all candidate genes was significantly associated with risk in both sexes. This finding suggests that this polymorphism may be a marker of blood pressure response during exercise.
chromosome 9p21.3 effect on CDKN2A/2B gene expression profiling in patients with myocardial infarction localized the CDKN2A/2B protein expression within the inner wall of the coronary plaques. This finding suggests a potential role for these genes in the pathogenesis of atherosclerosis.

Purpose: Coronary artery disease is significantly influenced by genetic background. Genome-wide association studies showed that common genetic variants in the linkage disequilibrium on chromosome region 9p21.3 are associated with ischemic heart disease. However, the mechanistic basis for this association is still obscure. Aim of this study was to investigate the influence of rs231293 genotype on the transcript abundance of two neighbouring genes CDKN2A/B and the risk for coronary artery atherosclerosis.

Methods: Human atherosclerotic plaques were obtained from a cohort of 30 patients with ischemic heart disease. Coronary artery stenosis was isolated from 20 patients who underwent heart transplantation for post-ischemic dilated cardiomyopathy. Genetic analysis was performed on atherectomy material and vascular smooth muscle cell (VSMC) isolated from coronary arteries. Total RNA and gDNA were extracted using the semi-automated platform Maxwell 16 and total RNA were reverse transcribed using a high-capacity cDNA Archive Kit. SNP rs1333040 was genotyped using quantitative RT-PCR. Correlation among these variables was determined by univariate and multivariate analysis. Immunostaining for CDKN2A/B was performed using primary antibodies against CDKN2A/B, and the expression was quantified using a digital image analysis system.

Results: Genotype distribution of rs1333040 in atherosclerotic plaques was as follows: 5 had no risk allele (CC), 10 had one (CT) and 15 had two (TT). The expression of CDKN2A/B2B genes was significantly lower in the TT plaques than in the plaques without the risk allele (CC), whereas their expression in the CT plaques was intermediate (p < 0.001). Genotype distribution of rs1333040 in coronary arteries was the following: 4 had no risk allele (CC), 2 had one (CT) and 14 had two (TT). Expression analysis on VSMC revealed that the expression of CDKN2A/B genes for both genotypes is basically the same as according to the rs1333040 genotype (p = 0.001 for both genotypes). Immunohistochemical staining on coronary artery section localized the CDKN2A/B2 gene expression within the VSMC.

Conclusion: Our findings show a link between rs231293 genotype and CDKN2A/B2B gene expression in diseased human coronary arteries, which support the hypothesis that sequence variations in the CAD risk interval on 9p21 may act as distant regulatory sequences and be required for the correct vascular expression of CDKN2A/B2B.
Results: After conditional analysis, among 34 variants exceeding significance threshold and located all near the adenomodulin gene, GWAS identified 2 variants, rs2957692 (p=1.5 x 10^-13) and rs2957717 (p=2.4 x 10^-10) independently associated with 9p21 in this LAMD study. Together the 2 SNPs of the epitope showed 1.4-fold (P=1.2 x 10^-4) increase in the allele frequency of rs2957692 and 4.5-fold (P=3.2 x 10^-8) after adjusting for non-genetic correlates. Age (p=1.6 x 11), female gender (p=2.9 x 17), body mass index (p=8 x 150), smoking (p=3.0), Plasma levels of creatinin (16.0E), CRP (11.1E), NtProBNP (2.0E), Interleukine-10 (1.5E), Interleukine-1 receptor antagonist (2.6E) and CTProteinaseEndothelin-1 (1.2E) were identified as independent non-genetic correlates of MRproADAM levels accounting together for 70% (69-72) of its variance. CTProteinaseEndothelin-1 was the most important source of variance accounting alone for 43% (40-45). All genetic and non genetic variables remained independently associated to MRproADAM levels in the multivariable model (table) accounting for 72% (70-73) of its variance.

Conclusions: MRproADAM levels increase in association with endothelial aggression, cardiovascular risk factors, hemodynamic status and inflammatory processes. Although MRproADAM levels’ variance is dominantly related to non-genetic factors, genetic variants near the ADAM gene also affect such levels.

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Results: Plasma concentrations of MMPs were significantly increased in patients rather than control subjects (MMP-1, 7.00±1.84 vs. 1.11±0.17; MMP-2, 3.44±1.11 vs. 1.33±0.13; MMP-3, 4.18±1.03 vs. 1.00±0.17; MMP-9, 15.45±3.19 vs. 16.6±0.55 respectively). Gel zymography revealed 43, 66, and 83 kDa molecular weight bands which consistent with active MMP-1, -2, -3, and -9 respectively exhibiting gelatin-degrading activity in both patient and control subjects. Comparison of the patients with AMI and control subjects demonstrated that in patient subjects, MMP-9, -1, -2, and -2 activity was 13-fold, 6-fold, 4-fold, and 3.5-fold higher respectively than in control samples. No up-regulation of mRNA expression was found.

Conclusions: To our knowledge, it is the first monitoring of MMP gene and protein expression and also circulating active MMPs in Iranian patients with AMI and normal subjects. Up-regulation of MMPs activity is common in the failing myocardium and missing up-regulation of transcription indicates that protein levels of MMPs were regulated at the post transcriptional level.
Influence of rs5065 atrial natriuretic peptide gene variant on Coronary Artery Disease

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Either modified ANP plasma levels or peptide structural alterations have been involved in development of cardiovascular events. To investigate the impact of rs5065 atrial natriuretic peptide (ANP) gene variant on coronary artery disease (CAD) and its outcomes and to gain potential mechanistic insights on the association with CAD.

Methods: 1004 patients undergoing coronary angiography for suspected CAD (432 stable angina (SA), 572 acute coronary syndrome (ACS)) were genotyped for rs5065 ANP gene variant. Data in SA and ACS groups were replicated in an independent population of 482 SA patients (rSA) and of 675 ACS patients (rACS), respectively. Clinical follow-up was available for both SA and rSA patients. Plasma NT-proANP, myeloperoxidase (MPO), lipoprotein-associated phospholipase A2 (Lp-PLA2), oxidized low density lipoprotein (oxLDL), were assessed in a subgroup of rSA patients.

Results: rs5065 minor allele (MA) was an independent predictor of ACS (OR=1.90; 95% CI: 1.40-2.58, p<0.001). At follow-up, rs5065 MA was independently associated with significantly higher rate of major adverse cardiovascular events (MACE) in SA group, p<0.001. Data were replicated in rSA group at follow-up (p<0.008). Cox proportional hazard analysis tested by 4 models confirmed higher MACE risk in rs5065 MA carriers in both SA and rSA cohorts. Significantly higher MPO levels were detected in rs5065 MA carriers (597±345-832 vs. 488±33-612, p=0.038). No association of rs5065 was observed with NT-proANP levels.

Conclusions: The MA of rs5065 ANP gene variant associates with increased susceptibility to ACS and has unfavorable prognostic value in CAD.

Coronary artery disease risk polymorphisms in Latvian patients and population controls

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Purpose: Genome-wide association studies (GWAS) have discovered multiple single nucleotide polymorphisms (SNP) associated with coronary artery disease (CAD). These results are generally based on populations of Northern and Western European ancestry and importance and informativeness of the results may be limited for researchers studying patients of other ethnic backgrounds. Our aim was to validate findings of European CAD GWAS in Latvian population which is of Eastern European ancestry. We focused on six loci: 1p13.3, 2q28.3, 6q25.1, 9p21.1, 10q11.21 and 15q22.33 characterized by SNPs rs598893, rs2943634, rs692269, rs1333049, rs501120 and rs17728212 respectively.

Methods: All six SNPs were genotyped in a case-control study consisting of 1100 clinically diagnosed CAD cases and 452 population controls with no history of cardiovascular manifestations. Written informed consent was obtained from all participants of this study. Genomic DNA was extracted from white blood cells by chloroform-phenol method and genotyped using fluorescently labeled hydrolysis probes in a real-time PCR system.

Results: Two of the investigated polymorphisms rs2943634 and rs1333049 were significantly associated with CAD. Allele C of the rs1333049 had frequency 0.522 and 0.437 in controls and cases respectively (CAD OR=1.40; 95% CI: 1.20-1.64; P=2.12e-5). None of other four SNPs reached significance level of P<0.05 even before correction of results. Significant CAD-variant (rs5065) differences were observed between average of nine GWAS (studying populations of Western European origin) reported previously and our Eastern European sample for rs2943634 (MAF controls 0.342 vs. 0.477, respectively; P=0.0003) and rs17728212 (MAF controls 0.276 vs. 0.230 respectively; P=0.035).

Conclusion: Our findings suggest that rs1333049 is strongly associated with CAD risk in population from Latvia and that rs2943634 also increases risk of CAD. Further we found evidence that MAF difference of SNPs among regions within Europe is significant, therefore making interpretations based on other population samples challenging.

GENETICS AND GENE THERAPY

Effectiveness of genetic studies in inherited cardiomyopathies

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Introduction: Genetic diagnosis in inherited cardiomyopathies is still limited and reimbursement policies are lacking. There is need to evidence the cost of genetic testing and know their profitability in order to establish criteria for priorising access to genetic testing for these diseases.

Methods: We determined the cost per positive genotyping (CPG) in 234 index cases with diagnosis of HCM, ARVC, LQTS, and Brugada Sdr (BS). The genetic tests of the most prevalent genes were included (MYH7 and MYBPC3 for HCM: PKP2, DSP, DSC2, DSG2, PKG for ARVC; KCNQ1, KCNH2, SCN5A, KCNEM1, KCNEM2, KCNJ2 for LQTS; and CSN5A for BS). Genetic studies expenses were HCM 1300 €, ARVC 2050 €, BS 725 €, LQTS 1750 €. Estimation of the cost of periodical screening in wildtype relatives (WT) were calculated from 10-60 yrs (ECG 20 €, echocardiogram 60 €, cardiac consultation 40 €). Frequency of the clinical screening of relatives was based on the International Cardiology Society guidelines. For HCM and ARVC a 20% penetration rate was assumed, for LQTS 10% and for BS 5%.

Results: In HCM the CPG was 186,960 € (1.40, 95% CI: 1.20-1.64, P=2.12e-5). None of other four SNPs reached significance level of P=0.05 even before correction of results. Significant CAD-variant (rs5065) differences were observed between average of nine GWAS (studying populations of Western European origin) reported previously and our Eastern European sample for rs2943634 (MAF controls 0.342 vs. 0.477, respectively; P=0.0003) and rs17728212 (MAF controls 0.276 vs. 0.230 respectively; P=0.035).

Conclusion: Our findings suggest that rs1333049 is strongly associated with CAD risk in population from Latvia and that rs2943634 also increases risk of CAD. Further we found evidence that MAF difference of SNPs among regions within Europe is significant, therefore making interpretations based on other population samples challenging.
Adenovirus-mediated gene transfer of a luciferase reporter gene by a cardiac-specific promoter through direct injection into the left ventricular wall

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P4932

**Early AAV9-mediated over-expression of S100A1 ameliorates myocardial hypertrophy in dystrophin-deficient mice**


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Mutations of dystrophin leading to a complete loss of the protein cause x-chromosomal Duchenne muscular dystrophy (DMD), frequently associated to severe cardiomyopathy (CMP). However, although cardiac complications increase in severe cardiac deficiency of these patients, strategies to efficiently treat the CMP are not well established. It has been suggested that the loss of cardiomyocyte Calcium (Ca²⁺) cycling integrity plays a key role in the development and progression of CMPs, although so far its role in dystrophin-associated CMPs is unclear. In this context, the cardiomyocyte EF-hand Ca²⁺-sensor protein S100A1 plays a critical role in regulating Ca²⁺ cycling integrity and has been considered for potential therapeutic approaches to treat CMP. We have investigated the efficiency of Adeno-associated virus serotype 9 (AAV9)-mediated cardiac over-expression of S100A1 to prevent the development of CMP in dystrophin-deficient (mdx) mice. Therefore, AAV-9 vectors containing S100A1 cDNA under transcriptional control of a CMV-MLC promoter (AAV9/S100A1) were created. 1012 AAV9/S100A1 vector particles were intravenously injected into 8 week-old mdx mice before the onset of CMP. AAV9 harboring an enhanced green fluorescent protein reporter (AAV9/EGFP) was used as a control vector. At the age of 1 year histological examinations, echocardiography and PV-loops were performed to assess myocardial morphology and contractility (cardiomyocyte cross-sectional areas (csa; μm²), enddiastolic posterior wall thickness (PWTd; mm), fractional shortening (FS%; and left ventricular maximum rate of pressure change (dp/dtmax; mmHg/sec).

Uninjected and AAV9/EGFP-treated mdx mice showed distinct myocardial hypertrophy and reduced contractility (csa 860±71 and 871±39 μm²; PWTd 1.7±0.1 and 1.53±0.06 mm; FS 49±4% and 51±4% and dp/dtmax 562±230 and 529±304 mmHg/sec, respectively) compared to age-matched wildtype mice (csa 329±13 μm²; PWTd 1.1±0.1 mm; FS 74±3% and dp/dtmax 1235±933 (values ± standard error)). AAV/S100A1/1001-treated mdx mice showed significantly reduced myocardial hypertrophy (csa 0.33±0.3 m² and PWTd 1.14±0.07 mm, respectively). PV loops showed improved contractility (dp/dtmax 1497±406 mmHg/sec; p<0.05) in AAV/S100A1/1001-treated mdx mice, whereas fractional shortening did not improve significantly (FS 54±2%).

Our data suggest that AAV9-mediated cardiac overexpression of S100A1 attenuates myocardial hypertrophy in mdx mice thereby representing a valuable tool to limit cardiac dysfunction in dystrophin-deficient cardiomyopathy.

P4933

**Post-infarct treatment with microRNA145 reduces myocardial infarct size and improves cardiac remodeling and function in rabbits**

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Background: It has been reported that micro RNA 145 (miRNA145) inhibits proliferation of vascular smooth muscle and progression of atherosclerosis. However, it is not still unclear whether miRNA145 is involved in ischemia-reperfusion injury. Objective: We investigated the involvement of miRNA145 in ischemia reperfusion injury and investigated whether post-infarct treatment with miRNA145 has a cardioprotective effect in a rabbit model of myocardial ischemia and reperfusion. Methods: Male Japanese white rabbits underwent 30 min of coronary occlusion followed by 6 hours and 14 days of reperfusion. Rabbis were then sacrificed with overdose of pentobarbital and the hearts were removed. From the myocardial tissues, miRNA145 expression levels relative to RNU6B were obtained at 6 hours and 14 days after myocardial infarction. In another series of experiments, rabbits underwent 30 min of coronary occlusion and 14 days of reperfusion. Rabbits then received intravenous injection of saline (control group, n=5) or 0.05 mg/kg of miRNA145 en, respectively) versus liposome (miRNA145 group, n=6) immediately after reperfusion. At 14 days after MI, rabbits were sacrificed and the hearts were removed. The area at risk and infarct areas were measured by Evans blue dye and TTC staining, respectively. The infarct size was calculated as a percentage of the risk area of the left ventricle.

Results: Expression of miRNA145 was significantly increased in the border area compared with the infarction and non-infarction areas of the myocardium at 6 hours after myocardial infarction. However, the increase in miRNA145 expression in the border area was significantly attenuated at 14 days after myocardial infarction. Post-infarction treatment with miRNA145 significantly reduced the myocardial infarct size (16.7±3.7%) as compared to the control (31.8±2.7%) at 14 days after myocardial infarction. The miRNA145 also improved LV dimensions and improved dp/dt.

Conclusions: It is suggested that miRNA145 is involved in the regulation of ischemia reperfusion injury and post-infarction treatment with miRNA145 is protective against ischemia-reperfusion injury.

P4935

**Identification of AAV as most efficient vector for transvascular gene transfer into porcine myocardium based on in vitro model for prediction of the cardiac gene transfer performance**


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Background: Adeno-associated virus (AAV) mediated gene transfer into diseased myocardium holds high promises for numerous gene therapy applications. While high transfer efficiencies are achieved in small rodents, gene transfer to the hearts of larger animals appears to be limited. Aim of our work was the development of a method to improve gene transfer into porcine myocardium.

In contrast to a non-viable porcine myocardium, a cell line derived from a porcine myocardium is highly applicable to predict in vivo transfer efficiencies. Therefore, a new transvascular cardiac gene transfer system was investigated. AAV vectors carrying the firefly luciferase gene under the control of the cardiac troponin I promoter were directly injected into the left heart cavity of a porcine heart using ultrasound facilities. Luciferase expression was monitored for 28 days through light emission in vivo bioluminescence imaging system (IVIS, Xenogen) and in vitro luciferase assays. Myocardial infarction was induced immediately before direct injection.

Results: Luciferase expression was evident within 12 h after AD-Tnl or AD-CMV- luciferase injection. At 24 h post-injection, strong luciferase expression was still observed. In addition, myocardial infarction induced higher luciferase expression in the AD-Tnl-Luc group but not the AD-CMV-Luc group. Luciferase assays in multiple organs in vivo confirmed that luciferase expression was higher in the CMV group (Panel B, p<0.01 vs Tnl group).

Conclusions: Ad serotype 6 combination with a cardiac specific promoter (cardiac troponin I) is highly efficient for cardiac gene transfer, as evident by high-level expression for 28 D and more cardiac specific, especially under the myocardial infarction condition.
opment of an in vitro model to facilitate development of vectors for cardiac gene transfer in large animals and for future clinical trials.

**Methods:** To identify the most suitable in vitro model, luciferase reporter constructs driven by the CMV promoter have been cross-packaged into the capsids of AAV serotypes 1-6, 8 and 9. These constructs have been tested for their gene transfer efficiency in isolated cardiomyocytes and/or 300 μm organotypic myocardial slices of mice, rats and pigs. After the models had been validated for rodents, we analyzed gene transfer efficiency into the porcine heart with the two most promising vectors from the porcine in vitro study and AAV9, the most efficient serotype in mice. In order to facilitate cardiac gene transfer, vectors were applied via retroinfusion into the coronary venous system of pigs.

**Results:** Both isolated cardiomyocytes as well as organotypic slices revealed strong transgene expression after transduction with certain serotypes, while others failed almost completely to mediate transgene expression. Isolated cells and organotypic slices led to similar results, with AAV6 being most efficient for rat and pig. Comparison between the mouse, rat and porcine in vitro models showed that species differences are evident in vitro. Furthermore, comparison of reporter activities in the pig in vivo revealed that AAV6 enables the most efficient cardiac gene transfer followed by AAV5, while AAV9 was 300-fold less efficient than AAV6, confirming the predictions of the in vitro model.

**Conclusion:** We have developed in vitro models that show valuable prediction power for the efficiency of cardiac gene delivery of AAV vectors, allowing us to improve gene transfer delivery to the porcine heart 300-fold compared to AAV9. The correlation with published rodent in vivo data and our porcine in vivo data in this study underscores the feasibility of both models (primary cardiomyocytes and organotypic slices) for in vitro vector assays. The predictive power of the models unveiled two AAV serotypes more than suited for cardiac gene transfer in the pig than AAV9, the most efficient vector for cardiac gene transfer in mice.

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**P4936**

**R14Del, a Dutch phospholamban mutation in Spanish family. Genotype-phenotype aspects**

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**Introduction:** The sarcoplasmic reticulum Ca(2+)-pumping proteins are key regulators of cardiac contractility, and alterations in sarcoplasmic reticulum Ca(2+) cycling properties have been shown to be causal of familial cardiomyopathies. Through genetic screening of dilated cardiomyopathy patients, we identified a previously described deletion of arginine 14 (PLN-R14Del) in the coding region of the phospholamban (PLN) gene known to cause dilated, arrhythmogenic right ventricular and non-compaction cardiomyopathy. The mutation is located in a conserved domain of phospholamban and consists of a loss of 3 nucleotides (AGA) leading to loss of the R14 residue but not a change in reading frame.

**Methods:** The index case was a 29 year old woman presented with syncopal episodes. She was referred for genetic counseling. ECG at baseline and drug challenge test. Drug challenge test allowed to unmask a higher proportion of female silent carriers.

**Results:** Seven of the 9 patients studied were mutation carriers although only 2 of them met diagnostic criteria of dilated cardiomyopathy: the proband and her asymptomatic 78 year old maternal grandmother. Five of the 7 carriers' ECG showed strikingly low voltage QRS complexes, despite no echocardiographic abnormalities in 3 (mother and 2 maternal aunts). Apart from proband all carriers were asymptomatic with no history of arrhythmia evidenced. Of note, proband's father belongs to another family affected by Hypertrophic cardiomyopathy, although the father himself only express mild left ventricular hypertrophy with normal ECG. R14Del mutation has been described in 40 families to date. There is information available from 68 carriers. Recently, this mutation has been identified as a mutation with bender effect in up to 14% of cases in a cohort of Dutch patients with dilated and arrhythmogenic cardiomyopathy. Carriers from this cohort characterized by low voltage QRS and negative T waves in leads C4 and D1, similar to R14Del carriers.

**Conclusion:** Low voltage ECG has a high sensitivity to identify PLN mutation carriers. Sarcoplasmic reticulum Ca(2+)-pumping phenotype can be mild or normal in most carriers of R14Del mutation who can remain asymptomatic throughout life. Severe phenotype can be consequence of double mutations. Interpretation of genotype-phenotype correlations should be done in the context of large family trees and complete cardiac evaluation.
Association of a matrix metallopeptidase 1 gene polymorphism with long-term outcome of thoracic aortic aneurysm

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Objective: Although genetic variants are thought to contribute to the development of thoracic aortic aneurysm including dissection (TAA), it remains unclear whether gene polymorphisms are associated with the long-term outcome of TAA.

Identification of genetic variants related to the long-term outcome of medically treated TAA may lead to a better understanding of the factors relevant to the progression or rupture of TAA, and consequently may better inform the selection of patients as candidates for surgical therapy because of a higher risk of rupture. The purpose of the present study was to identify genetic variants associated with the long-term outcome of medically treated TAA in patients with TAA.

Methods: A total of 103 medically treated patients with TAA (age, 63.3 ± 11.9 years; 13 aneurysms and 90 dissections) were retrospectively studied for their outcomes (mean follow-up period, 24 months). An unfavorable outcome was defined as: (1) death from cardiovascular causes or aneurysm rupture, (2) operation, (3) conversion to surgical repair, or (4) the occurrence of cardiovascular events after initial hospitalization.

Results: The prevalence of Stanford A, hypertension, prior cardiac surgery, shock, and a maximum aneurysm diameter were greater in subjects with the unfavorable outcome of TAA than in those with the favorable outcome of this condition. Evaluation of genotype distributions by the chi-square test and subsequent multivariable logistic regression analysis with adjustment for covariates revealed that the presence of the polymorphism (rs514921) of the matrix metalloproteinase 1 gene (MMP1) was significantly (P = 0.0167) smaller in the combined group of the AG and GG genotypes for this polymorphism (42.3 ± 11.9%) than in subjects with the AA genotype (48.8 ± 11.2%). Kaplan-Meier survival curves constructed according to MMP1 genotypes showed a more favorable outcome of TAA (log-rank P = 0.0146) in subjects with the AG or GG genotypes.

Conclusion: The G allele of rs514921 in MMP1 is associated with favorable long-term outcome of TAA. Determination of genotypes for this polymorphism may prove informative for assessment of the long-term outcome of TAA.

CONCLUSION OF THE STUDY

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Conclusion: The G allele of rs514921 in MMP1 is associated with favorable long-term outcome of TAA. Determination of genotypes for this polymorphism may prove informative for assessment of the long-term outcome of TAA.
Subclinical hyperthyroidism and cardiovascular mortality


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Background: It is still uncertain if subclinical hyperthyroidism and “high-normal” thyroid function is a risk-factor for cardiovascular mortality.

Objectives: To examine the risk of cardiovascular death in relation to subclinical hyperthyroidism.

Methods: Patients consulting their general practitioner from 2000–2009 in Copenhagen, Denmark, who underwent thyroid blood tests, were identified by individual-level linkage of nationwide registries. Patients with a history of thyroid disease or related medication were excluded. Risk of cardiovascular mortality was analyzed using Kaplan-Meier curves and Poisson regression models to estimate Incidence Rate Ratios (IRR).

Results: Of 525,100 individuals in the study population (mean age 51.7 years [SD ±18.0]; 39.5% males) 504,113 (96.0%) were euthyroid, 1,474 (0.3%) had clinical hyperthyroidism, 2,173 (0.4%) had subclinical hyperthyroidism, and 17,379 (3.3%) had clinical hyperthyroidism and 5,414 (1.0%) subclinical hyperthyroidism. An increased risk of cardiovascular mortality was found in two levels of subclinical hyperthyroidism (TSH <0.1, 0.1–0.2 mU/L and normal Free-T4): IRR 1.14 [95%CI: 1.03–1.28], IRR 1.20 [1.05–1.37] and in “high-normal” levels of euthyroidism (TSH 0.2–0.4 mU/L; IRR 1.16 [1.09–1.25].

Conclusions: Subclinical hyperthyroidism and “high-normal” thyroid function is a significant risk-factor for cardiovascular mortality.

Endothelial Microparticles derived under high Glucose concentrations increase monocyte adhesion on endothelial cells through upregulation of adhesion proteins in a p38 dependent way

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Background: Circulating endothelial microparticles (EMP) are increased in diabetic patients, but their role in the progression of atherosclerosis is unclear. We tested the hypothesis if EMP isolated from glucose treated human coronary endothelial cells (HCAEC) influence adhesion protein expression in target endothelial cells and thereby increase adhesion of monocytes to the endothelium, an important step in the development of atherosclerosis.

Methods and results: We created a hyperglycemic condition by treating HCAEC for 72h with 30 mM Glucose and generated EMP after 24h starvation. These modified EMP were defined as “injured” EMP (IEMP). Confocal microscopy, flow cytometry and electron microscope were used to characterize size (~1μm) and cellular origin of IEMP. The effects of IEMP were compared with EMP generated from untreated HCAEC. IEMP, but not EMP, induced upregulation of ICAM-1 and VCAM-1 in target HCAEC demonstrated by Western Blot and real-time RT-PCR. Moreover, Western Blot experiments revealed that IEMP treated with IEMP expressed ICAM-1 and VCAM-1 in a time- and dose-dependent way. Following experiments showed increased monocyte adhesion on IEMP-treated HCAEC compared to EMP-treatment and control (47.3% vs. 26.9% vs. 8.4%, p<0.05). We next investigated how EMP activate endothelial cells and found that pro-inflammatory cytokines IL-8, IL-6, TGF-β and MCP-1 were detectable in EMP. EMP contain higher level of TGF-β (807 ng/ml vs. 1647 ng/ml, p<0.05) and IL-8 (115 pg/ml vs. 33 pg/ml, p<0.05) than EMP. As cytokines mentioned above activate p38 into phosphorylated p38 (phospho-p38), expression of p38 activity was analyzed in HCAEC after IEMP stimulation. Time dependent experiments revealed that IEMP induced activation of p38 into phospho-p38 in HCAEC within 30 min. Inhibition of p38 by p38-specific inhibitor reduced adhesion proteins on HCAEC and promotion of monocyte adhesion on target cells.

Conclusion: Endothelial Microparticles from glucose treated cells increase monocyte adhesion by altering adhesion protein expression in endothelial cells. Activation of p38 through proinflammatory cytokines containing MP might be a possible pathway.

Effects of combined genotypes for polymorphisms of the apolipoprotein A-V gene and the butyrophilin, subfamily 2, member A1 gene on metabolic syndrome in east Asian populations

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Purpose: Although recent genome-wide association studies have implicated several loci and genes in predisposition to metabolic syndrome (MetS) in Caucasian populations, the genes that confer susceptibility to this condition in Asian populations remain to be identified definitively. We previously showed that the −1131T→C polymorphism (rs627799) of the apolipoprotein A-V gene (APOA5) and the C→T polymorphism (rs6928464) of the butyrophilin, subfamily 2, member A1 gene (BTN2A1) were significantly associated with an increased serum concentration of triglycerides, a decreased serum concentration of HDL-cholesterol, and the prevalence of MetS in Japanese individuals. The purpose of this study was to examine whether these polymorphisms synergistically affect the prevalence of MetS in East Asian populations.

Methods: The study population comprised 3474 Japanese (2744 subjects with MetS, 730 controls) and 1671 Korean (1294 subjects with MetS, 377 controls) individuals. Subjects with MetS had three or more of the five components of criteria for MetS, whereas control individuals had none of the five components. Bonferroni’s correction was applied for statistical significance of association.

Results: Comparison of allele frequencies by the chi-square test revealed that rs627799 of APOA5 was significantly associated (P = 0.025) with MetS in Japanese and Korean individuals, whereas rs6928464 of BTN2A1 was significantly associated with MetS in Japanese individuals, but not in Korean individuals. Similar analysis of combined genotypes for rs627799 of APOA5 and rs6928464 of BTN2A1 revealed that the prevalence of MetS was significantly (P < 0.0056) increased in Japanese individuals with the C allele of APOA5 and any genotypes of BTN2A1 as compared to those with the TT genotype of APOA5 and the CC genotype of BTN2A1. There was no relation detected between combined genotypes and MetS in Korean individuals. Multivariable logistic regression analysis with adjustment for age and sex revealed that rs662799 of APOA5 and rs6928464 of BTN2A1 were significantly (P < 0.01) associated with MetS in Japanese individuals, but not in Korean individuals. Similar analysis of combined genotypes with adjustment for age and sex revealed that individuals with the C allele of APOA5 and the T allele of BTN2A1 had a 2.87-fold increased risk for MetS compared to those with the TT genotype of APOA5 and the CC genotype of BTN2A1 in Japanese individuals. There was no relation between combined genotypes and MetS in Korean individuals.

Conclusions: Genetic variants of APOA5 and BTN2A1 may synergistically affect the prevalence of MetS in Japanese individuals.

Clinical and prognostical implication of advanced glycation in acute coronary syndromes

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Aims: Advanced glycation end products (AGEs) are molecules with important
pathophysiological implications in cardiovascular pathology. The aim of our study was to evaluate the prognostic value of AGEs and its soluble receptor (sRAGE) in the context of acute coronary syndrome (ACS), both in in-hospital phase and follow-up period.

Methods: AGE and sRAGE were analyzed by fluorescence spectroscopy and competitive ELISA (respectively) in 215 consecutive ACS patients admitted to coronary care unit (62±13.0 years, 24.2% female). 47.4% had a diagnosis of ST segment elevation myocardial infarction. The end-points were the development of cardiac events (cardiac deaths, reinfections and new-onset heart failure) during in-hospital phase and follow-up period (366 days, interquartile range: 273-519 days).

Results: The mean fluorescent AGEs and sRAGE levels were 57.7±45.1 AU and 1045.4±850.0 pg/mL, respectively. 19 patients presented cardiac events during in-hospital phase and 29 during the follow-up. In-hospital cardiac events were significantly associated with higher sRAGE levels (P=0.001), but not long-term cardiac events (P=0.365). Regarding fluorescent AGE the opposite was happened. After multivariate analysis correcting for sex, left ventricular ejection fraction, glucose levels, hemoglobin, GRACE and SYNTAX scores, sRAGE was significantly associated with in-hospital prognosis whereas fluorescent AGEs was significantly associated with long-term prognosis (figure 1: by quartiles of fluorescent AGE).

Conclusion: We conclude that elevated values of sRAGE are associated with worse in-hospital prognosis, whereas high AGE levels are associated with more follow up events.

P4947

Acute cardiac ryanodine receptor loss-of-function leads to bradycardia, arrhythmia, heart failure and transcriptional metabolic reprogramming

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Rationale: The cardiac ryanodine receptor Ca2+ channel (RyR2) plays a central role in excitation-contraction coupling. RyR2-mediated Ca2+ flux into mitochondrial also controls metabolism, stimulates TCA cycle flux and aerobic metabolism, and atypical cell death in other cell types. Cardiac RyR2 levels can be reduced up to 50%, with age and in disease states such as heart failure, ischemia and diabetes. Objective: We tested whether a similar, controlled depletion of cardiac RyR2 proteins sufficient to recapitulate the pleiotropic events associated with heart failure.

Methods and Results: We report that conditional Ry2 knockout mice (cRy2KO) rapidly exhibit bradycardia, arrhythmia, heart failure and transcriptional metabolic reprogramming.

Conclusions: These findings provide new insights into the role of RyR2 in cardiac physiology and disease.

P4948

Genetic deficiency of corticotropin releasing hormone influences cardiac function through fatty acid metabolism

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Purpose: We have previously shown that Corticotropin Releasing Hormone (CRH)-null (Crh-/-) mice have compromised cardiac capacity, demonstrated by their reduced FS (%) and EF (%) values compared to wild-type (Crh+/+) mice; this effect is exaggerated by acute administration of LPS in non-lethal doses. We investigated whether this effect is due to changes in fatty acid (FA) metabolism, since the heart relies mostly on FA to fulfill its energy needs.

Methods: Endotoxemia was induced by L.P. LPS administration (120µg/g animal).

Cardiac function was assessed by 2D M-mode echocardiography, basally and 20hrs after LPS. Fatty acid metabolism related gene expression was studied by real time PCR.

Results: At basal state, significantly reduced mRNA levels of PPARα, PPARγ, FAS and CD36 by 37% (P<0.05), 62% (P<0.05), 40% (P<0.05) and 70% (P<0.05) were found in the myocardium of Crh-/- compared to the Crh+/+ mice. LPS administration resulted in downregulation of myoccardial perilipin a peroxisome proliferator activator receptor (PPAR) α, PPARγ, PPARγ coactivator (PGC)-1a and AMPKα2 mRNA levels by 66% (P<0.01), 44% (P<0.05), 50% (P<0.05) and 58% (P<0.05) respectively. In Crh-/- mice LPS administration caused further downregulation of PPARα, AMPKa2 as well as carnitine palmitoyltransferase (CPT)-βb levels. As we have previously reported, Crh-/- mice demonstrate significantly compromised ability to survive the above LPS challenge. To assess whether support of PPARs function via administration of PPAR ligands would rescue the detrimental effects of LPS administration in Crh-/- mice, we i.p. injected both Crh+/+ and Crh-/- mice with the PPARγ ligands pioglitazone and rosiglitazone (3mg/kg/day), or the non-specific PPAR agonist bezafibrate (50mg/kg/day) for 7 days prior to LPS administration. Neither pioglitazone nor rosiglitazone treatment had any effect on the reduced myocardial capacity or survival of Crh-/- given LPS. However, indices of cardiac function were improved in all bezafibrate-treated Crh-/- mice and their survival rate 24 hours after LPS administration was indistinguishable from that of the Crh+/+ mice.

Conclusion: We have shown that genetic Crh deficiency is characterized by impaired myocardial FA metabolism, most likely through inhibition of the PPARα effects.

P4949

CD40L deficiency ameliorates diet-induced adipose tissue inflammation, but does not protect from insulin resistance and hepatic steatosis in mice

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Background: Adipose tissue inflammation fuels the metabolic syndrome. We recently reported that CD40L – an established marker and mediator of cardiovascular disease – induces inflammatory cytokine production in adipose cells in vitro. Here, we tested the hypothesis that CD40L deficiency modulates adipose tissue inflammation in vivo.

Methods and Results: WT or CD40L-/- mice consumed a high fat diet (HFD) for 20 weeks (n=15 per group). Inflammatory cell recruitment was impaired in mice lacking CD40L as shown by a decrease of adipose tissue macrophages, B-cells, and an increase in protective T-regulatory cells. Mechanistically, CD40L-deficient mice expressed significantly lower levels of the pro-inflammatory chemokine MCP-1 both, locally in adipose tissue and systemically in plasma. Moreover, levels of pro-inflammatory IgG-antibodies against oxidized lipids were reduced in CD40L-/- mice. Accordingly, CD40L deficiency partially protected from weight gain and fat deposition in the early stages of diet-induced obesity (DIO). Also, circulazong-low density lipoprotein and insulin levels were lower in CD40L-/- mice. However, CD40L-/- mice consuming HFD were not protected from the onset of insulin resistance and hepatic steatosis, suggesting that CD40L selectively limits the inflammatory features of diet-induced obesity rather than its metabolic phenotype. Interestingly, CD40L-/- mice consuming a low fat diet (LFD) showed both, a favorable inflammatory and metabolic phenotype characterized by diminished weight gain, improved insulin tolerance, and attenuated plasma adipokine levels.

Conclusion: We present the novel finding that CD40L deficiency limits adipose tissue inflammation in vivo. These findings identify CD40L as a potential mediator at the interface of cardiovascular and the metabolic disease.
Stress-induced adipose inflammation promotes a proinflammatory state and impairs insulin sensitivity by adipocyte-derived monocytic chemotrafactor protein-1

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Objective: Stressors contribute to thrombosis and perturbation in glucose metabolism. Since adipose inflammation is also involved in obesity-induced insulin resistance and thrombotic disease, we tested the hypothesis that stress correlates with adipose inflammation.

Research Design and Methods: Male mice were subjected to daily restraint stress for 2 weeks. Inguinal white adipose tissue (WAT) was collected from control and stressed mice to examine CD11b-positive cells and expression of macrophage markers (CD68 and F4/80), proinflammatory cytokines (MCP-1, TNF-α, and IL-6), adiponectin, and coagulation factors (PAI-1 and tissue factor (TF)) using immune-histochemistry and RT-PCR, respectively. Glucose metabolism was assessed by glucose (GTT) and insulin tolerance tests, and expression of IRS-1 and GLUT4 in WAT. To examine the effects of MCP-1 blockade, animals were intraperitoneally transplanted with control- or TNF (dominant negative form of MCP-1)-overexpressing adipose-derived stromal cells (ADSCs). Plasma fatty acid (FFA), mouse MCP-1, TNF-α, and IL-6 levels were measured.

Results: Stress increased accumulation of CD11b-positive cells and expression of CD68 and F4/80 in WAT. The stressed mice also showed a higher frequency of smaller adipocytes in the inguinal adipose tissue compared to the control mice. Chronic stress also induced proinflammatory cytokine expression including MCP1, TNF-α, and IL-6 and reduced adiponectin. Furthermore, stressed mice showed increase in FFA, MCP-1, TNF-α, and IL-6 concentration. The stress-induced adipose inflammation worsened the prothrombotic state through induction of PAI-1 and TF. Without any changes in GTT, stress worsened insulin sensitivity and decreased IRS-1 and GLUT4 in WAT. 7ND-ADSCs reversed the stress-induced adipose inflammation with reduction of CD11b-positive cells, macrophage markers, and proinflammatory cytokines. Moreover, 7ND-ADSC treatment rescues the stress-induced decline in insulin sensitivity and the prothrombotic state.

Conclusions: Restraint stress over a 2-week period evoked the expression of MCP-1 and other inflammatory adipokines in adipose tissue and a low-grade chronic state of adipose inflammation that exacerbated insulin resistance and induced the procoagulant factors through the expression of MCP-1. MCP-1 inhibition with 7ND-ADSCs reversed adipose inflammation and these pathological consequences. Increased lipolysis and FFA would be also involved in stress-induced adipose inflammation.

P4953

The heme oxygenase system reduces pericardial adiposity and improves diabetic cardiopathy in Zucker diabetic fatty rats

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Visceral adiposity adversely affects many vital organs including the heart. We investigated the effects of the heme oxygenase (HO) inducer, hemin, on pericardial adiposity and diabetic cardiopathy in Zucker diabetic fatty rats (ZDF), and age-sex-matched Zucker-lean controls.

Hemin administration normalised glyceric levels in ZDF rats and suppressed pericardial adiposity with the reduction of pro-inflammatory oxidative mediators including, NF-κB, c-Jun-N-terminal kinase (cJNK), endothelin-ET1, TNF-α, interleukin (IL)-6, IL-1β, and β-isoprostane. Similarly, hemin reduced the pro-inflammatory macrophage-M1 phenotype, but increased the M2-phenotype that dampens inflammation in the heart, and improved cardiac hemodynamics by enhancing ejection fraction, stroke volume, cardiac output, while reducing total peripheral resistance. Hemin improved glucose metabolism by potentiating insulin-signaling agents like the insulin-receptor substrate-1 (IRS-1), phospholipidinosinst-3-kinase (PI3K), glucose-transporter-2 (GLUT2) and protein-kinase-B (PKB). The hemin effects were accompanied by increased HO-activity, whereas the HO-blocker, stannous-meso-epoxyserin (SnMep) nullified the effects. Interestingly, the hemin effects were less pronounced in Zucker-lean controls with healthy status, suggesting greater selectivity in ZDF with disease. Since NF-κB activates TNF-α and IL-1β, while TNF-α and JNK impair insulin-signalling, the high levels of these cytokines in obesity/diabetes would create a vicious cycle that together with β-isoprostane and ET1 exacerbates tissue injury, compromising its function. Therefore, the concomitant reduction of proinflammation cytokines and macrophage infiltration coupled to increased levels of IRS-1, GLUT2, PI3K, PKB and cardiac hemodynamics may account for enhanced glucose metabolism, and improved cardiac function in ZDF. We conclude that HO-inducers may be explored against the co-morbidity of impaired insulin-signalling, visceral adiposity and diabetic cardiopathy.

P4954

Synergistic effect of human immunodeficiency virus and the metabolic syndrome on arterial stiffness

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Purpose: Patients with Human Immunodeficiency Virus (HIV) on combination antiretroviral therapy have a high incidence of the metabolic syndrome (MS) and cardiovascular (CV) disease. To determine the contribution of HIV infection and the MS to vascular disease, we investigated aortic stiffness using aortic pulse wave velocity (PWV) in HIV patients with and without the MS.

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The metabolic syndrome significantly affects the association between resting heart rate and all cause as well as cardiovascular mortality. When patients without the MS have increased PWV compared to controls. The increase in PWV observed with HIV alone is similar to that seen with the MS alone. The detrimental impact of HIV and the MS on PWV appears to be synergistic. Given the increased prevalence of the MS in HIV patients, therapeutic interventions aimed at controlling this increased risk may reduce HIV-related vascular disease.

Methods: Subjects were divided into: 1) HIV-ve/MS-ve (n=84), 2) HIV-ve/MS-ve (n=35), 3) HIV+ve/MS-ve (n=73) and 4) HIV+ve/MS+ve (n=17) according to the National Cholesterol Education Program-Adult Treatment Panel III guidelines. Magnetic resonance imaging was used to assess aortic PWV between the ascending aorta at the level of the pulmonary artery (PA) and descending aorta 11 cm below the PA. PWV was calculated as \( \Delta x / \Delta t \) (distance between the 2 imaging levels)/(time delay between the arrival of the pulse wave between these imaging levels). To compare PWV in groups 1-4, one-way ANOVA analysis was performed with post hoc Bonferroni correction.

Results: PWV was 16% higher in HIV+ve/MS+ve and 14% higher in HIV+ve/MS-ve subjects compared to HIV-ve/MS-ve subjects (6.26±1.73 vs 5.38±1.00 m/s, p=0.042 and 6.14±1.91 vs 5.38±1.00, p=0.032 respectively, Figure 1). HIV+ve/MS+ve subjects had 21% higher PWV compared to HIV-ve/MS-ve subjects (7.43±2.43 vs 6.14±1.93, p=0.028).

Conclusion: HIV patients without the MS have increased PWV compared to controls. The increase in PWV observed with HIV alone is similar to that seen with the MS alone. The detrimental impact of HIV and the MS on PWV appears to be synergistic. Given the increased prevalence of the MS in HIV patients, therapeutic interventions aimed at controlling this increased risk may reduce HIV-related vascular disease.
Multi compartment body composition analysis in chronic heart failure: air displacement plethysmography, body impedance analysis, dual-energy X-ray absorptiometry, and 3D white-light scan analysis

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Purpose: Chronic Heart Failure (CHF) is characterized by impaired body fluid distribution and associated with obesity and cachexia. Early recognition of changes in body composition is vital for optimal adjusted medical therapy and has high prognostic relevance for patients suffering from CHF. Prospective data on body composition in CHF is sparse. We investigated whether Body composition can be as adequately assessed by Air-Displacement Plethysmography (ADP) and Bio-electrical Impedance Analysis (BIA) as by the current gold-standard Dual-X-Ray Absorptiometry (DXA) and Magnetic Resonance Imaging (MRI).

Methods: In this single centre, prospective, observational study we included 52 consecutive symptomatic NYHA II, IIa, outpatient, who presented with HFrEF and left ventricular ejection fraction (LVEF) <40% of their body weight. The body weight was determined with a digital balance with a precision of ±0.1 kg. Height and arm circumference were measured by standardized procedures. FM analysis was obtained by DXA, ADP, and BIA. Intracellular and extracellular status was assessed by BIA. Anthropometrics was performed by 3D-BodySurfFace-White-Light Scan (3DS).

Results: 52 CHF patients participated (11 female). In HFrEF (n=33) mean age was 66.4±5.3, BMI was 27.9±4.5, mean FM 32.0% ± 9.1, mean LVEF was 70.4±6.1, mean BMI was 30.0±5.5, mean FM was 34.8% ± 8.6. Lin’s Concordance Correlation Coefficient (CCC) for FM in DXA vs ADP was 0.76 (95% CI 0.64-0.85) and by BIA 0.89 (95% CI 0.54-0.85). The mean percentage of extracellular fluid measured by BIA was 45.0% (CI 95% 40.4-44.9) and in HFrEF vs 46.1% (CI 95% 45.1-47.1) in HIFEF, which differed significantly (P<0.039); consequently percentage of intracellular body fluid was 55% (CI 95% 54.1-55.9) in HFrEF vs 44.0% (CI 95% 44.0-44.9) in HFrEF, which differed significantly (P=0.039); consequently percentage of intracellular body fluid was 55.0% (CI 95% 54.1-56.0) in HFrEF and significantly different (P=0.039). Thus, percentage of intracellular body fluid was significantly higher in patients with CHF vs healthy volunteers.

Conclusions: FM analysis can be accurately assessed by ADP and BIA in heart failure with reduced and preserved ejection fraction and healthy volunteers. Furthermore, body composition analysis differences in HFrEF vs HIFEF were significantly higher compared to HFrEF with respect to FM, FFM and body fluid distribution, independent of the prevalence of oedema or body fluid status.

These results show that OF induces metabolic, oxidative and functional disturbances but also a higher susceptibility to cardiac functional damage after ischaemia ex vivo. Complementary data are required to understand the cellular pathways involved in these cardio-metabolic and oxidative modifications.

## Longitudinal study of Advanced Glycation End products plasma levels in patients undergoing coronary artery bypass grafting surgery: effects of statin treatment, gender and type 2 diabetes

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The accumulation of advanced glycation end products is thought to be a key factor in the initiation and progression of type 2 diabetes. Despite studies demonstrating a beneficial role of statins in reducing cardiovascular morbidty/mortality risk with type 2 diabetes, studies may also raise the risk of type 2 diabetes in the elderly. We aimed to show an association between plasma AGE levels and statin therapy in 17 diabetic patients (11 male, 6 female) mean age 63.59 years ± 5.79 (SD) and 10 non-diabetic patients (8 male, 2 female) mean age 65.60 years ± 6.39 (SD) all in sinus rhythm undergoing coronary artery bypass grafting (CABG) surgery with cardiopulmonary bypass (CPB).

Our longitudinal model (pre- and post- CABG) was adjusted for cross – clamp time (non-significant) and for differences in diabetes status, gender and treatment with statin. Plasma AGE (μg/mL) was assayed by enzyme-linked immunosorbent assay (ELISA).

AGE plasma levels were higher in non diabetic compared to diabetic patients pre- (64.1±26.2 vs 47.6±21.1 μg/mL, p<0.05) and post- (33.1±12.6 vs 14.7±5.1 μg/mL, p<0.05) CABG. Taking into account gender differences, non diabetic females vs males had increased AGE plasma levels pre- (108±70.8 μg/mL vs 39.5±12.4 μg/mL, p<0.01) and post-(57.5±39 vs 21.9±6.9 μg/mL, p<0.05) whereas, diabetic males had higher AGE plasma levels pre- (58.4±27.4 vs 22.4±21.6) and post- (16.6±5.6 vs 10.4±4.5 μg/mL, p<0.05).

CABG induced a drop in AGE plasma levels independent of diabetes or gender. Non diabetic and diabetic pts on statin therapy vs no therapy had higher AGE levels pre- and post- CABG. Female diabetics experienced a significant drop in AGE plasma concentrations after CABG, a similar significant drop happens after CABG in female patients not treated with statins. In pts not under statin treatment the post CABG drop in AGE plasma concentrations was significantly higher in non diabetics vs diabetic patients, a reduction 3- to 4-fold higher than the significant reduction for pts treated with statins (diabetic and non-diabetic). AGE plasma levels significant reduction post-CABG in patients with statins was on average almost 50-fold the post-CABG reduction in patients not submitted to statin treatment. The significant mean reduction of post-CABG AGE plasma levels was not different in magnitude between diabetic and non diabetic pts.

Statin and diabetes treatment may contribute to gender differences in AGE plasma levels pre- and post- CABG and may have a similar effect in limiting the post-CABG drop of AGE plasma levels in female patients.

**FULL APPRAISAL OF GLYCEMIC RISK**

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Purpose: Patients with acute coronary syndromes (ACS = unstable angina/myocardial infarction) and newly detected impaired glucose tolerance (IGT) or type diabetes (T2DM) have beta-cell dysfunction. The hypothesis that a DPP-4 inhibitor can be safely instituted soon after an ACS and will improve beta-cell function was tested.

Methods: ACS patients with IGT or T2DM (n=71), screened by oral glucose tolerance tests (OGTT) 4-23 days (median 6) after admission were randomised to sitagliptin 100 mg (n=34) or placebo (n=37) during 12 weeks. All patients received lifestyle advice but no other glucose lowering drugs. The endpoints were beta-cell function assessed through OGTT expressed as insulinogenic index (IGI = Insulin30/30-Glucose30) and Acute Insulin Response to glucose (AIRg) by a frequently sampled intravenous glucose tolerance test (FSIGT).

Results: Sitagliptin was well tolerated. Fasting glucose (Figure 1c) and insulin resistance (Figure 1d) did not change during the 12 weeks of treatment in either group. Significantly more patients in the sitagliptin group normalised their post glucose levels after sitagliptin than in the placebo group (26 vs. 16; p=0.004). The IGI and AIRg at baseline did not differ between the sitagliptin and placebo groups (69.9 vs. 66.4 µmol/ml/min and 1394 vs. 1106 µmol l−1 min−1). After 12 weeks the IGI was 85.0 in the sitagliptin and 58.1 µmol/ml/min in the placebo group (p=0.019;
Detection of subclinical left ventricular dysfunction in asymptomatic young adults with type-2 diabetes: a cardiac magnetic resonance study

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Introduction: There is an epidemic of obesity and Type 2 diabetes (T2DM) in the developed world. Although diabetic cardiomyopathy is well documented in older adults with T2DM there is very little data on younger adults and no published CMR data.

Objective: To use CMR to assess whether asymptomatic young adults with T2DM have evidence of subclinical left ventricular (LV) dysfunction compared to healthy lean and obese controls.

Methods: 40 asymptomatic subjects (20 T2DM, 10 obese non-diabetic controls, 10 lean non-diabetic controls) underwent CMR assessment of the LV on a Siemens Avanto 1.5T system. LV function and volumes were assessed using SSFP. Circumferential strain was assessed using a multi-breed HCTSPAMM tagging sequence at 3 slices (basal, mid-cavity, apical). Perfusion was assessed on first-pass contrast imaging during adenosine stress.

Results: Subjects were matched for age, height and blood pressure. Global peak early diastolic strain rate (PEDSR) was significantly lower in T2DM, compared to lean and obese controls (Table 1). There was no evidence of coronary artery disease on perfusion testing.

Conclusions: This is the first CMR study demonstrating subclinical diastolic dysfunction in asymptomatic young adults with T2DM. The significant difference between the T2DM and obese groups suggest that T2DM in early adulthood has detrimental effects on cardiac function, additional to those associated with obesity.

P4965 Heart rate variability, postprandial responses of glucose and insulin and beta-cell function: the NEO study

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Introduction: Low heart rate variability (HRV) is associated with diabetes mellitus (DM). We hypothesize a negative association of HRV with insulin resistance in fasting state (IR) and postprandial responses of glucose and insulin and a positive association with beta-cell function.

Methods: Baseline analysis of the Netherlands Epidemiology of Obesity (NEO) study, including 6000 individuals aged 45-65y with a BMI (kg/m2) ≥ 24 mmol/L. IR was calculated as SDNN (ms), RMSSD (ms), LF (ms2) and HF (ms2). Blood was sampled fasting, 30min and 150min after a mixed meal (400 ml, 600 kcal). We calculated Homeostasis Model Assessment of insulin resistance (HOMA2-IR) as a measure IR. Area under the curve (AUC) for glucose and insulin were used as measures of the postprandial responses. Beta-cell function was calculated with the insulinogenic index (IGI: Δinsulin(30-10)/Δglucose(30-0)) and AUC/IACG. Linear regression analysis was used to assess the association of HRV with IR, postprandial responses and beta-cell function, stratified by day/night and adjusted for sex, age, BMI, waist circumference, ethnicity, education, smoking, medication, hypertension, beats per minute and physical activity.

Results: Of 4562 included participants, 639 had HRV measurements. Participants with recordings <72h (n=75), CVD (n=43) or DM (n=47) were excluded, resulting in 489 participants (46% men, mean age (SD): 56 (6) years, BMI: 31 (4) kg/m2, fasting glucose: 5.6 (0.78) mmol/L. We found no association of lnSDNN (ms) during daytime with HOMA2-IR (ρ=0.15, 95%CI: -0.32, 0.03),
Diabetes is related to higher central blood pressure

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Background: Central blood pressure (BP) is directly related to LV overload as well as blood supply to the heart and brain. It may also directly damage coronary and cerebral arteries and lead to heart attacks. Several studies have shown higher prevalence of end-organ damage and central than peripheral BP. Central BP is also shown to better predict cardiovascular (CV) risk. Diabetes is related to at least two-fold increased in CV risk. The influence of diabetes on central BP values is unknown.

Aim: To assess the independent influence of diabetes on the ascending aortic BP values.

Methods: BP in the aorta was measured using fluid-filled filter in 400 patients (200 with type 2 DM and 200 without DM matched for age and gender) undergoing non-emergency coronary angiography. Brachial BP was measured using a sphygmomanometer. Both groups did not differ in respect of age and sex. General regression model (age, sex, mean BP, risk factors, LVEF, creatinine level, and drugs were included into the model) was used to assess the independent influence of diabetes on BP.

Results: Systolic, diastolic, and mean brachial BP did not differ between the study groups (138.6±21.3 vs. 133.7±20.3 mmHg; p=0.06; 83.4±12.0 vs. 82.6±10.7 mmHg; p=0.081; 109.1±14.0 vs. 99.6±13.0 mmHg; p=0.27 in diabetics and non-diabetics resp.) but brachial pulse pressure was higher in diabetics (55.4±15.3 vs. 51.1±14.2; p=0.02). Central BP values were shown in the Table. In multivariable analysis diabetes was related to higher ascending aortic systolic BP by 2.7% (95% confidence intervals: 1.7-3.8 mmHg) and pulse pressure by 4.1 (2.5-6.7) mmHg as well as higher brachial pulse pressure by 1.8 (0.2-3.3) mmHg. The differences in mean and diastolic (both brachial and central) BP as well as brachial systolic BP were not significant in multivariable analysis.

Conclusions: Diabetes is independently related to higher values of systolic and pulse pressure in the ascending aorta. This may partly explain the higher CV risk in diabetics.

Omentin-concentrations predict 10-year incidence of diabetes in Thai: the EGAT study, 1998-2008

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Background: Obesity has reached pandemic proportions and is an established risk factor for insulin resistance, type 2 diabetes (T2D) and cardiovascular disease. Altered secretion of adipokines in obesity is believed to contribute to the undesirable changes in glucose metabolism that ultimately result in the development of T2D. Omentin-1 is a novel adipokine preferentially produced by adipose tissue with insulin-sensitizing effects, where the circulating levels are decreased in insulin-resistant state.

Objective: To investigate whether baseline omentin-1 concentrations were associated with 10-year incidence of diabetes in Thais.

Materials and Methods: Nested case-control study was conducted in a population-based cohort: the Electricity Generating Authority of Thailand study, 1998-2008. The baseline demographic, anthropometric and clinical data were collected in 1998. The resurvey was done 10 years later in the same participants. one hundred and sixty eight individuals with newly diagnosed diabetes and 168 age-, sex- and with similar clinical characteristics to those in the study. baseline serum omentin-1 concentrations were measured by ELISA.

Results: Baseline socioeconomic status, educational background BMI, and waist and hip circumferences were significantly higher in incident cases compared with control. omentin-1 concentrations were significantly negatively correlated with BMI (r=-0.196, P<0.0001) and waist circumference (r=-0.168, P=0.002) newly di-agnosed diabetes group had significantly lower omentin-1 concentrations compared with control group (437.4±149.4 vs. 483.6±172.1 mg/mL; P=0.007) even after further adjusting for family income, educational background, smoking, drinking, family history of diabetes, and waist circumference (p=0.019) Hazard ratios (95%CI) for developing diabetes for those in the highest tertile vs. lowest tertile of omentin-1 concentrations were 0.506 (0.297-0.863) and 0.528 (0.298-0.935) in unadjusted and multivariate adjusted model, respectively.

Conclusions: In the present study, high baseline concentrations of omentin-1 were found to be associated with a substantially reduced risk for incident diabetes over 10 years follow up in a cohort of initially healthy middle-aged Thais and the observed association was independent of obesity.
Results: Of 857 participants, 231 (27%) had prediabetes. Compared to normoglycemic subjects, prediabetics were significantly older (40 vs 38 years, p=0.0002), more often male (57 vs 43%, p<0.001), and they had a higher body mass index (BMI) (24.9 vs 23.9 kg/m², p<0.001). The prevalence of active smokers among prediabetic and normoglycemic subjects was 29% and 19%, respectively (p=0.0003), with a median (interquartile range) number of pack years among current smokers of 11.5 (5.8-18.8) and 5.9 (3.8-13.5), respectively (p<0.001). In age- and sex-adjusted logistic regression models using prediabetes as the outcome variable, current smoking was significantly associated with prediabetes (Odds ratio (OR) 1.79 (95% confidence interval 1.24-2.59), p=0.002). Former smoking was not significantly related to prediabetes [OR 0.76 (95% CI 0.51-1.13), p=0.18]. Compared to never and past smokers, current smokers with <5, 5 to 10 and >10 pack years had an OR (95% CI) of 1.07 (0.53-2.13), p=0.86; 2.09 (1.08-4.07), p=0.03; and 2.22 (1.34-3.68), p<0.002, respectively.

Conclusion: Accumulating as few as 5-10 pack years of smoking carries a more than 2-fold increased risk of having prediabetes in healthy young adults. Thus, our data reinforce the importance of smoking cessation in the general population.

P4970 Membrane type 1-matrix metalloproteinase correlates with the coronary plaque stability in patients with postprandial hyperglycemia

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Background: We reported pericellularly localized membrane-type matrix metalloproteinases (MT-MMPs), which are main activator of secreted latent type MMPs, were highly expressed on circulating peripheral blood mononuclear cells (PBMCs) from patients with acute myocardial infarction (AMI). Although, postprandial hyperglycemia (PPH) is an independent risk for development of cardiovascular disease, there are few knowledge about predictor of coronary plaque in type 2 diabetic patients with PPH.

Methods: Fifty eight outpatients with type 2 diabetes whose glycated hemoglobin (HbA1c) ranged between 5.5 and 8.0 (JDS%), and 1.5-2.0 mmol/l (HDL-C), as a short-term marker for PPH did not exceed 14 μg/ml, were enrolled. PBMCs from each subject underwent 64-detector computed tomography to analyze the plaque. Vulnerable plaque was defined as positive remodeling (remodeling index > 1.05), low-attenuation plaque (< 39 Hounsfield Units), and/or adjacent spotty calcification. PBMCNs were examined for the frequencies of CD14 positive cells expressing MT1-MMP using flow cytometry. Serum levels of MMPs, pentraxin-3 were measured by using ELISA methods.

Results: The prevalence of vulnerable plaque was 19 patients (33%), MT1-MMP expression on PBMCNs in all patients with PPH was significantly elevated in compared to normal subjects without PPH. In patients with vulnerable plaque, MT1-MMP expression was higher than that in without plaque (36.4±10.5% vs 25.7±10.3%, p<0.012), but no differences in HbA1c serum MMP-2, 9, and plasma pentraxin-3 levels.

Conclusion: The elevated MT1-MMP expression on PBMCNs is associated the existence of vulnerable plaque in type 2 diabetic patients with PPH. These finding suggested that the measurement of MT1-MMP on PBMCNs may become a new predictor of vulnerable plaque in postprandial hyperglycemia patients.

P4971 Prognostic impact of concomitant occurrence of metabolic syndrome and chronic kidney disease in patients undergoing coronary intervention; involvement of coronary plaque morphology

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Background: In the present study, we aimed to assess the impact of metabolic syndrome (MetS) and chronic kidney disease (CKD) on atherosclerotic plaque and cardiovascular outcomes.

Methods and Results: A total of 204 consecutive patients who underwent percutaneous coronary intervention (PCI) were enrolled. They were divided into four groups according to the presence or absence of MetS and CKD. MetS was defined by following criteria of the National Cholesterol Education Program in Adult Treatment Panel III. CKD was defined as an estimated GFR <60 ml/min/1.73 m².

Results: The prevalence of MetS was 66.7% and of CKD was 46.2% as compared to the other three groups during follow-up period (Log rank p=0.029). In the IB-VUS analyses, patients with both MetS and CKD showed a greater plaque burden (p<0.001) with larger lipid contents (p<0.048) as compared to the other three groups. The incidence of cardiovascular death, nonfatal myocardial infarction, target lesion revascularization, and revascularization for new lesion as well as coronary plaque characteristics using integrated backscatter intravascular ultrasound (IB-VUS) showed a greater incidence in patients with both MetS and CKD (46.2%) as compared to the other three groups.

Conclusion: The administration of alogliptin significantly improved postprandial endothelial dysfunction and increase in triglyceride, suggesting alogliptin may be a promising antiatherogenic agent.
has been suggested to be the mediating mechanism. We tested if change in maximum heart rate (ΔMHR) through seven years predicts NOG over 28 years.

**Methods:** Exercise MHR was measured among 3,387 healthy men at two separate examinations, in 1972 and in 1979. The men were divided into quartiles (Q1-Q4) by ΔMHR. NOG events were registered in a nationwide survey of all participants’ hospital charts through 2008. Relative risk of NOG in the quartiles was calculated using Cox proportional hazard regression adjusting for baseline MHR, maternal diabetes, smoking status, systolic blood pressure, fasting triglycerides, fasting blood glucose, age, BMI, physical fitness and change in physical fitness.

**Results:** A total of 124 NOG events were registered. Median MHR at baseline was 165 and 160 seven years later. The incidence of NOG was the highest among the men who decreased their MHR the most (Q1) and lowest among those who increased their MHR (Q4). Q1 was associated with an 82% increased NOG risk compared with Q4.

**Conclusions:** These findings indicate that a reduction of MHR of more than 15 BPM over seven years is independently associated with a significantly increased long-term risk of new onset diabetes. We suggest that a marked fall in maximum heart rate could be associated with autonomic nervous system dysfunction. This observation could be helpful when identifying individuals at high risk of developing diabetes.

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**P4975**

**Autonomic neuropathy is independently associated with new heart failure and atrial fibrillation in diabetic patients with preserved ejection fraction: prognostic significance of heart rate recovery**

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**Purpose:** Atrial fibrillation (AF) and heart failure (HF) are important and interacting complications of type 2 diabetes mellitus (T2DM), and may be predicted by left atrial volume index (LAVI). Diabetic autonomic neuropathy may be an important contributor to AF, and may be evidenced by attenuated heart rate recovery (HRR). We sought whether HRR had an association with HF and AF in T2DM, independent of LA size.

**Methods:** We enrolled 814 consecutive uncomplicated patients with T2DM (56±11 yrs, 508 men) who had negative stress echocardiography from 2004 to 2007. Patients with prior cardiac surgery, AF, mild valvular disease, HF, ejection fraction <50% or any cancer at enrollment were excluded. Demographics, clinical assessment, standards of diabetes care, comorbidities, and treatment with insulin, diuretics, beta-blockers, statins, ace-inhibitors and aspirin were collected prospectively in 124 NOG events were registered. Median MHR at baseline was 165 and 160 seven years later. The incidence of NOG was the highest among the men who decreased their MHR the most (Q1) and lowest among those who increased their MHR (Q4). Q1 was associated with an 82% increased NOG risk compared with Q4.

**Conclusions:** HRR is associated with new onset HF and AF in T2DM, independent of LAVI. This association may reflect the contribution of autonomic neuropathy to both HRR and HF.

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**P4976**

**Low levels of IgM antibodies against phosphorylcholine are not associated with glucometabolic disturbances in patients with acute ST-elevation myocardial infarction**

E.C. Knudsen1, I. Seljeflot1, C. Muller2, G.B. Andersen1.

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**Purpose:** Phosphorylcholine (PC) is an important epitope on oxidized low-density
lipoprotein (oxLDL), and IgM antibodies against PC (anti-PC) are present as nat-ural antibodies in humans. Low levels of IgM anti-PC have been shown to be associated with an increased risk of myocardial infarction, indicating that PC may play an important role in the atherosclerotic process via oxLDL. oxLDL has proin-
flammatory properties and inflammation is important in the development of both cardiovascular diseases and diabetes.

The aim of the present study was therefore to elucidate a possible association between IgM anti-PC measured in-hospital and undiagnosed abnormal glucose regulation in patients with acute ST-elevation myocardial infarction (STEMI).

Methods: Patients (n=200, median age 58 (St.68) years) with a primary percu-
taneous coronary intervention (PCI) treated STEMI without known diabetes were included. Serum levels of IgM anti-PC were measured in-hospital and a stan-
dardized 75g OGTT (version plasma glucose measurements at 0 and 120 min) was performed at three-month follow-up. Based on the OGTT results, the patients were categorised according to the WHO criteria, and the term abnormal glucose regulation was defined as the sum of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes.

Results: A total of 50 patients were classified with abnormal glucose regulation at three-month follow-up. Median (25th, 75th percentiles) levels of IgM anti-PC in patients with abnormal vs. normal glucose regulation were 39.2 (23.7, 51.7) μU/ml vs. 41.5 (24.7, 59.7) μU/ml (p=0.55). Low levels of IgM anti-PC ≤ 24.6 μU/ml (25th percentile) were not associated with abnormal glucose regulation (OR 1.2 (95% CI 0.6, 2.6), p=0.57).

No significant correlations were found between IgM anti-PC and different glucose parameters (admission glucose, HbA1c, fasting glucose and 2-h glucose).

Conclusions: Low levels of IgM anti-PC were not associated with newly de-
tected abnormal glucose regulation in patients with acute STEMI without previ-
ously known diabetes. The previously reported association between low levels of IgM anti-PC and myocardial infarction seems to be independent of glucotoxic metabolic disturbances.

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**Chemerin is associated with the metabolic syndrome but is not linked to angiographically determined coronary artery disease**


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Purpose: The novel adipocytokine chemerin has been suggested to be linked to insulin resistance and to the metabolic syndrome (MetS). Its association with coronary artery disease (CAD) is unclear. We hypothesized that chemerin is as-
associated with both angiographically determined CAD and with the MetS.

Methods: We measured serum chemerin in 498 patients undergoing coronary angiography for the evaluation of established or suspected stable CAD; the MetS was defined according to NCEP-ATPIII criteria; significant CAD was diagnosed when coronary stenoses ≥50% were present.

Results: Chemerin was higher in MetS patients (n=150) than in subjects without the MetS (37 ± 15 vs. 31 ± 15 μU/ml; p=0.001). It did not differ significantly be-
tween patients with significant CAD (n=250) and those without significant CAD (p=0.327). When both, MetS and CAD status were considered, chemerin was higher in MetS patients both among those with significant CAD (188 ± 90 vs. 152 ± 60 μU/ml; p=0.002) and among those who did not have significant CAD (187 ± 73 vs. 148 ± 63 μU/ml; p=0.001); it did not differ significantly be-
 tween patients with significant CAD and subjects without significant CAD among MetS pa-
tients (p=0.248) nor among subjects without MetS (p=0.263). Analysis of covari-
ance (ANCOVA) showed that from the NCEP-ATPIII metabolic syndrome traits a large waist circumference as well as elevated triglycerides were independent predictors of elevated serum chemerin (F=12.5, p<0.001 and F=8.5, p=0.004).

Conclusions: We conclude that chemerin is significantly associated with the MetS but not with angiographically determined CAD. The overall association of chemerin with the MetS is carried by its association with visceral obesity and elevated triglycerides.

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**The J-shaped relationship between coffee consumption and prevalence of diabetes mellitus in the elderly population of Ikaria Island. Ikaria study**


University of Athens, Athens, Greece

Introduction: Scientific investigations have shown that caffeine can temporarily affect the number of EPCs. Importantly, we have shown that pioglitazone re-
moved CRP (2.5 ± 1.8 vs 1.5 ± 1.5 mg/dl, p=0.04) and ADMA levels (0.8 ± 0.5 vs 0.7 ± 0.5 μM, p=0.002). In addition, pioglitazone improved FMD (0.05 ± 0.02 vs 0.07 ± 0.04, p=0.04) and increased plasma concentrations of VEGF (102.7 ± 70.6 vs 169.3 ± 120.7 pg/ml, p=0.001). On the contrary, pioglitazone had no significant effect on CRP levels (p=0.57), FMD (p=0.34) and ADMA levels (p=0.16). However, pioglitazone administration increased significantly plasma levels of VEGF (126.3 ± 100.0 vs 163.2 ± 121.5 pg/ml, p=0.03), Moreover, both agents did not differ regarding to their effect on ΔEPCs (p=0.34), ΔFMD (p=0.70), ΔVEGF (p=0.27) and ΔCRP (p=0.85). Interestingly, we have found that pioglitazone had a superior effect than that of pioglitazone considering ΔADMA levels (0.16 ± 0.15 vs 1.5 ± 0.01), despite the non significant effect on ADMA levels resulting solely.

Conclusions: Our results support the beneficial role of pioglitazone in terms of inflammation and oxidative stress. In addition, the combined administration of pi-
oglitazone and perindopril could be proved beneficial with respect to angioene-
sis, as they both increase the plasma levels of VEGF in patients with diabetes, which may confer important pathophysiological and clinical implications.

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**Comparable effects of pioglitazone and perindopril on circulating endothelial progenitor cells, inflammatory process and oxidative stress in patients with diabetes mellitus**


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Purpose: Endothelial progenitor cells (EPCs) play a significant role in neovascular-
ization of ischemic tissues and in re-endothelialization of injured blood vessels. The purpose of this study was to investigate if the administration of pioglitazone or perindopril in diabetic patients can modify the number of EPCs in the peripheral blood and alter the endothelial function and inflammatory status of these patients.

Methods: Fifty type 2 diabetic patients were recruited and were randomly as-
signed to receive either pioglitazone (15mg/day) or perindopril (4mg/day) for a one-month period. Blood samples were obtained in order to count EPCs and infection markers such as C-reactive protein (hsCRP), vascular endothelial growth factor (VEGF) and asymmetric dimethylarginine (ADMA). Circulating EPCs were defined by the surface markers CD34+/KDR (CD34 and VEGFR2 express-
ing cells) and analyzed by flow-cytometry. Moreover the endothelial function of the patients was evaluated both on admission and after treatment with flow mediated dilation (FMD).

Results: We have found that neither pioglitazone (p=0.09), nor perindopril (p=0.5) affected the number of EPCs. Importantly, we have shown that pioglitazone re-
duced CRP (2.5±2.4 vs 1.8±1.5 mg/dl, p=0.04) and ADMA levels (0.8±0.5 vs 0.7±0.5 μM, p=0.002), both in treatment with pioglitazone improved FMD (0.05±0.02 vs 0.07±0.04, p=0.04) and increased plasma concentrations of VEGF (102.7±70.6 vs 169.3±120.7 pg/ml, p=0.001). On the contrary perindopril had no signifi-
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oglitazone and perindopril could be proved beneficial with respect to angiogene-
sis, as they both increase the plasma levels of VEGF in patients with diabetes, which may confer important pathophysiological and clinical implications.
Impact of exercise training on waist circumference, glucose metabolism and endothelial function in pre-diabetic, adipose patients with severe coronary heart disease

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Purpose: Certain fat-tissue-derived adipokines are thought to contribute to impaired glucose metabolism and endothelial dysfunction, which is a predictor of future cardiovascular events. The aim of our study was to elucidate the association between obesity and endothelial function of the left internal mammary artery (LIMA) in pre-diabetic patients with severe coronary heart disease (CHD), who were scheduled for elective coronary bypass grafting (CABG), and to investigate the influence of 4 weeks of regular physical exercise training (ET) in these patients.

Methods: 29 patients with CHD (age ≤75 years), obesity (BMI>28 kg/m²) and impaired glucose tolerance were randomized to 4 weeks of ET (in-hospital basis, 6 days a week for 20 min on a bicycle and rowing ergometer) (n=15) or sedentary lifestyle (n=14). At begin and after 4 weeks of ET, Fasting glucose, glycated hemoglobin (HbA1c), Metformin baseline/12mo, Sulfonylurea basel./12mo and Hx of Hypoglycaemia 12 months prior to enrolment were measured.

Conclusions: High-risk outpatients with type 2 diabetes and VD suffer from significant hypoglycaemias as complication of anti-diabetic therapy. Even after adjustment for differences in baseline characteristics and treatment, patients with VD have a significantly higher incidence of hypoglycaemia.

Comparison between the effects of ibradinidine and atenolol on heart rate variability in type II diabetic patients

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Purpose: Beta-blockers improve cardiac autonomic function in patients with type II diabetes and insufficient glycemic control on chronic oral antidiabetic mono- or dual combination therapy were enrolled to document patient characteristics, medical treatment as well as the prevalence of hypoglycaemia. We examined differences between diabetics with and without vascular disease in the duration of diabetes as compared to patients without manifest VD. No difference was found in baseline HbA1c as indicator of long-term glycaemic control, but patients with VD more often suffered from hypoglycaemia during the 12 months prior to enrolment. The retrospective data collection even underestimated the incidence of hypoglycaemias, as in the prospective 12 months follow-up the rate of hypoglycaemia increased to 22.8% in VD patients. Independent predictors of hypoglycaemia in VD were the treatment with sulfonylureas as well as with insulin.
amplitude, and also tended to improve SDNN and VLF amplitude, compared to placebo, although the latter differences did not achieve statistical significance.

Table 1

<table>
<thead>
<tr>
<th>RR interval (ms)</th>
<th>Aborted</th>
<th>Ibuprofen</th>
<th>Placebo</th>
<th>p*</th>
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<tbody>
<tr>
<td>Basal</td>
<td>746±68</td>
<td>704±53</td>
<td>759±89</td>
<td></td>
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<tr>
<td>Follow-up</td>
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<td>809±71</td>
<td>746±89</td>
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<td>SDNN (ms)</td>
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<td>107±26</td>
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<td>Follow-up</td>
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<td>103±35</td>
<td></td>
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<tr>
<td>SDNN (ms)</td>
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<tr>
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<td>39±10</td>
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<td>VLF amplitude (ms)</td>
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<td>34.6±12.0</td>
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<tr>
<td>LF amplitude (ms)</td>
<td>18.6±5</td>
<td>16.9±5</td>
<td>21.3±7</td>
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<tr>
<td>Basal</td>
<td>18.6±5</td>
<td>16.9±5</td>
<td>21.3±7</td>
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<tr>
<td>Follow-up</td>
<td>18.6±5</td>
<td>16.9±5</td>
<td>21.3±7</td>
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<tr>
<td>HF amplitude (ms)</td>
<td>18.6±5</td>
<td>16.9±5</td>
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<td>Basal</td>
<td>18.6±5</td>
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<tr>
<td>Follow-up</td>
<td>18.6±5</td>
<td>16.9±5</td>
<td>21.3±7</td>
<td></td>
</tr>
</tbody>
</table>

*p for changes among groups; ^p for changes <0.05 vs. placebo; #p for changes <0.01 vs. placebo.

Conclusions: In type II diabetic patients atorvastatin, as expected, significantly improved cardiac sympathetic-vagal balance. Interestingly, ibuprofen also showed some favourable effects on HRV variables, which deserves further assessment in larger studies, due to their potential clinical implications.

P4985

Hyperglycaemia-induced oxidative stress mediates monocyte dysfunction in diabetes mellitus

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Purpose: Monocytes play a very vital role in the biological process which increases the diameter of the existing arterial vessels. This process, also known as arteriogenesis, is essential for maintaining vascular integrity. Circulating monocytes are recruited to the sites of collateral growth where arteriogenesis is mediated through VEGF1 signalling pathways, among others. The impaired monocyte function in hyperglycaemia, due to the reduced ability of monocytes to respond to VEGF stimulation, has been implicated in reduced arteriogenesis in diabetes patients. Molecular mechanisms leading to this VEGF-specific site dysfunction defect in monocytes is incompletely understood.

Methods: Human monocytes were isolated from peripheral blood through gradient centrifugation and subsequent negative immunomagnetical isolation. THP-1 was used as the model monocyctic cell line. Expression of relevant molecules was detected by RT-qPCR and confirmed by Western blotting. Reactive oxygen species (ROS) was detected using Amplex Red and H2DFFA dye. Protein tyrosine phosphatase (PTP) activity was measured using pNPP substrate. VEGF-A induced monocyte chemotaxis was assessed in the modified Boyden chamber assay.

Results: The monocyte cell line THP-1 and primary monocytes isolated from healthy donors were subjected to normoglycaemia (5.5 mM glucose) or hyperglycaemia (25 mM glucose) for 7 days and 72 hours, respectively. Hyperglycaemia induced reactive oxygen species in the cells leading to a reduction in total PTP activity. Induced oxidative stress resulted in reduced VEGF-A induced chemotaxis. RT-qPCR analysis indicated that NADPH oxidase 2 (NOX2) is upregulated in hyperglycaemiated monocytes. Induced oxidative stress resulted in reduced VEGF-A-induced chemotaxis.

Conclusions: Our results reveal oxidative stress as a negative regulator of human monocyte function. Our results suggest that the hyperglycaemia-induced ROS in monocytes is mediated through NF-kB mediated NOX2 expression. Quenching of ROS generation can have positive effects on monocyte function.

P4986

Low rate of LDL-cholesterol target achievement in patients with type 2 diabetes with and without manifest vascular disease in Germany: results of DiaRegis

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Background: Patients with type 2 diabetes are at high risk for cardiovascular events. The new ESC/EAS guidelines for the management of dyslipidaemias recommend LDL cholesterol (LDL) not only <100mg/dl but even <70mg/dl. Little is known about the current lipid target achievement in diabetics in clinical practice in Germany.

Methods: In the DiaRegis registry, 3,740 consecutive outpatients with type 2 diabetes and insufficient glycemic control under chronic oral antidiabetic mono- or dual combination therapy were enrolled to document patient characteristics, medical treatment and prevalence of hypoglycemia. We examined differences between diabetics with and without vascular disease (VD), defined as known coronary artery disease (CAD) or prior stroke or peripheral artery disease (PAD) in the achievement of LDL targets.

Results: A total of 890 patients had known VD (17.9%, CAD, 4.7% prior stroke, 6.0% PVD). Type 2 diabetes outpatients with manifest VD were older, less often female and already had a significantly longer duration of diabetes. No difference was found in baseline HbA1c. Only 42.0% of the overall population were on statin treatment. 66.1% of diabetics with manifest VD and 34.3% of diabetics without known VD. Mean LDL was lower in diabetics with VD as compared to diabetics without known VD. The newly defined LDL target of <70mg/dl was reached in only 12.1% of diabetics with manifest VD and in only 5.2% of diabetics without VD.

Conclusions: Despite the high risk of subsequent cardiovascular events in type 2 diabetes less than half of the patients were treated with a statin. In very high risk diabetics with already manifest VD only 12.1% did reach the recommended target values of LDL <70mg/dl in clinical practice.

P4987

Can we predict the risk of glucose metabolism abnormalities in patients with previous percutaneous coronary intervention? - a comparison of patients with previous percutaneous coronary intervention and controls

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Background: Oral glucose tolerance test (OGTT) is recommended in all patients with coronary artery disease, since glucose metabolism abnormalities (GMA) adversely impact their prognosis. However, there are no risk models developed for the assessment of GMA in CAD patients. These models would be useful to identify patients with higher risk and to obviate the need of an OGTT in lower risk patients.

Purpose: To identify CAD related risk factors for GMA in patients with previous percutaneous coronary intervention (PCI).

Methods: 294 patients (mean age 60.9±10.9 years, 222 males), with previous PCI and without known diabetes were included. OGTT was performed according to WHO protocol and patients were classified, according to ADA criteria in normal (N), impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (DM). The relation between main epidemiological and CAD related factors was than evaluated.

Results: The OGTT identified 63 patients (21.4%) with IFG, 61 patients (20.7%) with IGT and 42 patients (14.2%) with DM. The prevalence of DM was 5.1% in the PCI group, vs. 5.5% in the control group (p=0.67). The percentage of patients with IGT was 12.4% in the PCI group, vs. 9.1% in the control group (p=0.36). The percentage of patients with IFG was 16.3% in the PCI group, vs. 10.7% in the control group (p=0.08).

Conclusions: Despite the high risk of subsequent cardiovascular events in type 2 diabetes less than half of the patients were treated with a statin. In very high risk diabetics with already manifest VD only 12.1% did reach the recommended target values of LDL <70mg/dl in clinical practice.
The influence of diabetes mellitus and hypertension on mid-term outcome of patients with Acute Myocardial Infarction in the era of Percutaneous Coronary Intervention

M.G. Lee1, M.H. Jeong1, M.J. Kim2, K.H. Lee1, K.H. Park1, D.S. Sim1, Y.J. Hong1, J.H. Kim1, Y. Ahn1, 1 The heart center of chonnam national university hospital, Gwangju, Korea, Republic of; 2The internal medicine of chonnam national university hospital, Gwangju. Korea, Republic of

Aims: The synergistic effect of diabetes mellitus (DM) and hypertension on mid-term outcome among acute myocardial infarction (MI) patients underwent percutaneous coronary intervention (PCI) is still controversial era. The aim of the present study was to assess the mid-term clinical outcomes among acute MI patients underwent PCI in relation to a history of hypertension or DM alone or a combination of the two.

Methods: Results: A total of 2,438 patients with acute MI underwent PCI who were included from January 2007 to November 2010 were studied. Patients were stratified into four groups according to the presence of DM or hypertension and followed up during 12 months period. The influence of cardiac risk factors, medications, angiographic findings, and interventional procedures were analyzed, and Cox proportional hazard analysis was used to determine the influence of hypertension and DM on major adverse cardiac events (MACE: death, recurrent MI, rehospitalization for CHF, requirement in male patients with DM).

In this study, in male patients, DM was an independent predictor of ACh induced CAS, and more intensive antianginal treatment would be required in male patients with DM.

Conclusion: In this study, in female patients, DM was an independent predictor of ACh induced CAS. But, in female patients, DM was not associated with ACh induced CAS. Therefore, gender difference must be considered in evaluating the predictor of ACh induced CAS, and more intensive antianginal treatment would be required in male patients with DM.

P4990

Prognostic impact of diabetes mellitus and hypertension for mid-term outcome of patients with Acute Myocardial Infarction in the era of Percutaneous Coronary Intervention

M.G. Lee1, M.H. Jeong1, M.J. Kim2, K.H. Lee1, K.H. Park1, D.S. Sim1, Y.J. Hong1, J.H. Kim1, Y. Ahn1, 1 The heart center of chonnam national university hospital, Gwangju, Korea, Republic of; 2The internal medicine of chonnam national university hospital, Gwangju. Korea, Republic of

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P4991

The influence of anemia on long-term prognosis in patients with acute myocardial infarction and concomitant glucose abnormalities

M. Mazurek1, J. Kowalczyk1, R. Lenarczyk1, T. Kurek1, A. Swiatkowski1, E. Jedrzejczyk-Pazest1, J. Gunprecht1, K. Strzej1, L. Polonski1, Z. Karunas1, 1Medical University of Silesia, 1st Dept of Cardiology, Department of Cardiometabolic Diseases, Zabrze, Poland; 2Medical University of Silesia, Silesian Center for Heart Diseases, 3rd Department of Cardiology, Zabrze, Poland

Background: Anemia deteriorates the prognosis in patients (pts) with myocardial infarction. However, the prognostic value of anemia in subjects with different glucose abnormalities (GA) and acute myocardial infarction (AMI) treated invasively remains unclear.

Aim: To assess the incidence and impact of anemia on clinical outcomes in subjects with different GA and AMI treated with percutaneous coronary intervention (PCI).

Methods: A prospective registry of 2154 consecutive AMI subjects treated with PCI was analyzed. In all hospital discharge and interpreted according to WHO criteria. This made it possible to divide the study population into 5 groups with different GA: diabetes mellitus (DM, n=360), new onset DM (n=298), impaired glucose tolerance (IGT, n=434), impaired fasting glycaemia (IFG, n=340), and control group (n=616). Anemia was defined using WHO criteria – hemoglobin level < 13 g/dl for men and < 12 g/dl for women. Cox regression was used to identify independent mortality predictors.

Results: The incidence of anemia in different glucose abnormalities was as follows: in DM (27.9%, n=99; new onset DM (23%, n=69); IGT (18.4%, n=80); IFG (16.4%, n=56); and in control group (14.7%, n=91). The long-term mortality in all AMI in-hospital survivors with anemia was significantly higher than in subjects without anemia (11.4 vs 5.5%, P<0.05). Further analysis with 15 and 24 months follow-up versus 28.8% vs. 37.0, Log-rank P<0.001. In multivariate analysis, hypertension and DM were a meaningful predictors of mid-term mortality, and the combination of two was a stronger predictor (hazard ratio = 1.790; 95% confidence interval = 1.313-2.442; P<0.001).

Conclusion: Acute MI patients with a history of DM or hypertension had a higher mid-term mortality than acute MI patients without such a history. The combination of DM and hypertension appeared to be more strongly associated with mortality than DM or hypertension alone.

P4991

The influence of anemia on long-term prognosis in patients with acute myocardial infarction and concomitant glucose abnormalities

M. Mazurek1, J. Kowalczyk1, R. Lenarczyk1, T. Kurek1, A. Swiatkowski1, E. Jedrzejczyk-Pazest1, J. Gunprecht1, K. Strzej1, L. Polonski1, Z. Karunas1, 1Medical University of Silesia, 1st Dept of Cardiology, Department of Cardiometabolic Diseases, Zabrze, Poland; 2Medical University of Silesia, Silesian Center for Heart Diseases, 3rd Department of Cardiology, Zabrze, Poland

Background: Anemia deteriorates the prognosis in patients (pts) with myocardial infarction. However, the prognostic value of anemia in subjects with different glucose abnormalities (GA) and acute myocardial infarction (AMI) treated invasively remains unclear.

Aim: To assess the incidence and impact of anemia on clinical outcomes in subjects with different GA and AMI treated with percutaneous coronary intervention (PCI).

Methods: A prospective registry of 2154 consecutive AMI subjects treated with PCI was analyzed. In all hospital discharge and interpreted according to WHO criteria. This made it possible to divide the study population into 5 groups with different GA: diabetes mellitus (DM, n=360), new onset DM (n=298), impaired glucose tolerance (IGT, n=434), impaired fasting glycaemia (IFG, n=340), and control group (n=616). Anemia was defined using WHO criteria – hemoglobin level < 13 g/dl for men and < 12 g/dl for women. Cox regression was used to identify independent mortality predictors.

Results: The incidence of anemia in different glucose abnormalities was as follows: in DM (27.9%, n=99; new onset DM (23%, n=69); IGT (18.4%, n=80); IFG (16.4%, n=56); and in control group (14.7%, n=91). The long-term mortality in all AMI in-hospital survivors with anemia was significantly higher than in subjects without anemia (11.4 vs 5.5%, P<0.05). Further analysis with 15 and 24 months follow-up versus 28.8% vs. 37.0, Log-rank P<0.001. In multivariate analysis, hypertension and DM were a meaningful predictors of mid-term mortality, and the combination of two was a stronger predictor (hazard ratio = 1.790; 95% confidence interval = 1.313-2.442; P<0.001).

Conclusion: Acute MI patients with a history of DM or hypertension had a higher mid-term mortality than acute MI patients without such a history. The combination of DM and hypertension appeared to be more strongly associated with mortality than DM or hypertension alone.

Table 1

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Std. Error</td>
</tr>
<tr>
<td>Sex</td>
<td>0.065</td>
<td>0.016</td>
</tr>
<tr>
<td>Mean Blood Glucose (mg/dl)</td>
<td>-0.051</td>
<td>0.050</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.036</td>
<td>0.038</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>-0.037</td>
<td>0.065</td>
</tr>
<tr>
<td>BMI</td>
<td>0.000</td>
<td>0.001</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
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<td>0.002</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.002</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Boys with T1D had higher cIMT than girls; moreover, cIMT correlated with weight and Body Mass Index (r=0.441; p=0.009), Insulin Units/kg (r= –0.346; p=0.045) and HbA1c (r=0.437; p=0.010); cIMT of boys only correlated with T1D duration (years) at a p-value of <0.05. In linear regression analysis sex remained the only significant independent predictor of cIMT (beta=0.459; p<0.001).

Conclusion: In this study, in male patients, DM was an independent predictor of ACh induced CAS. But, in female patients, DM was not associated with ACh induced CAS. Therefore, gender difference must be considered in evaluating the predictor of ACh induced CAS, and more intensive antianginal treatment would be required in male patients with DM.
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Purpose: Soluble CD40 ligand (sCD40L) is an inflammatory marker released by activated platelets and inflamed adipose tissue. Recent evidence suggests that sCD40L levels are higher in patients with metabolic syndrome. We sought to examine the relationship between chronically elevated sCD40L levels and insulin resistance by using the functional single nucleotide polymorphism (SNP) A3459G of the sCD40L gene.

Methods: The study population consisted of 265 individuals. After an overnight fast, a sample of blood was collected and used for biochemical measurements and genotyping. Plasma sCD40L levels were determined by ELISA. Plasma insulin levels were used to calculate insulin resistance by means of the Homeostatic Model Assessment (HOMA-IR). DNA was extracted from whole blood by using a commercially available kit and genotyping for the A3459G SNP of the sCD40L gene was performed by restriction fragment length polymorphism PCR method.

Results: In the study population, 188 individuals were carriers of the AA genotype, 44 of the AG and 33 of the GG genotype. Subjects exhibiting the GG genotype had significantly higher sCD40L levels when compared to AA and AG individuals (A). A trend towards an increase in the GG genotype was not significantly associated with fasting glucose levels (B), it was associated with higher insulin resistance, as calculated by HOMA-IR (C).

Conclusions: Our data show that chronically increased activation of platelets and the related inflammation of the adipose tissue releasing sCD40L, are associated with increased insulin resistance. Therefore, our study shows novel links between the CD40/CD40L axis and insulin resistance, providing novel insights into the pathophysiology of diabetes mellitus.

P4992 Genetic variability of sCD40L reveals a novel pathophysiological role of sCD40L in insulin resistance, in advanced atherosclerosis

P4993 Components of the interleukin-6 transsignalling system are associated with the metabolic syndrome, endothelial dysfunction and arterial stiffness

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Objective: The metabolic syndrome (MetS) is an increasing epidemiologic challenge and cardiovascular risk factor. IL-6 (IL-6) is a cytokine that exerts its biological function via a complex orchestration of soluble and membrane bound receptors. We have investigated associations between IL-6 and its soluble receptors, soluble IL-6-receptor (sIL-6r) and soluble glycoprotein 130 (sgp130) in the metabolic syndrome. Furthermore, we have investigated possible associations with endothelial dysfunction and arterial stiffness.

Methods: A total of 563 subjects were included in this study. Adult treatment panel III criteria of the national cholesterol education program were used for the definition of MetS. We used commercially available ELISA to analyze circulating levels of the markers. Pulse wave propagation time (PWP) was determined to assess arterial stiffness. The prevalence of CAD was 60% and 45% in DM and non-DM patients respectively (OR 1.6, p=0.001). The association of DM with CAD presence remained significant (OR 1.70, p<0.001) even after adjustment for differences in risk factors between DM and non-DM patients; DM patients were older, proportionally less smokers, more hypertensives, had higher body mass index and triglycerides and lower estimated glomerular filtration rate and HDL cholesterol compared to non-DM patients. In DM patients (n=413), independent predictors of CAD presence were fasting glucose levels (OR 1.008, p=0.001), male gender (OR 2.03, p<0.002) and hypertension (OR 2.01, p=0.017). In non-DM patients (n=657), independent predictors of CAD were age (OR 1.05, p<0.001), smoking (OR 2.21, p=0.013), male gender (OR 2.26, p=0.001), hypercholesterolemia (OR 2.69, p=0.001) and body mass index (BMI) (OR 2.03, p<0.001) and body mass index (BMI) (OR 2.03, p<0.001). The study population consisted of 265 individuals. After an overnight fast, a sample of blood was collected and used for biochemical measurements and genotyping. Plasma sCD40L levels were determined by ELISA. Plasma insulin levels were used to calculate insulin resistance by means of the Homeostatic Model Assessment (HOMA-IR). DNA was extracted from whole blood by using a commercially available kit and genotyping for the A3459G SNP of the sCD40L gene was performed by restriction fragment length polymorphism PCR method.

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Conclusions: Our data show that chronically increased activation of platelets and the related inflammation of the adipose tissue releasing sCD40L, are associated with increased insulin resistance. Therefore, our study shows novel links between the CD40/CD40L axis and insulin resistance, providing novel insights into the pathophysiology of diabetes mellitus.

P4994 Genetic susceptibility to type II diabetes in a Portuguese population

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Recently, variants in the transcription factor 7-like 2 (TCF7L2) gene have been reported to be associated with susceptibility to type 2 diabetes mellitus (T2DM) across multiple populations. There is no still replication in the Portuguese population, though.

Aim: Investigation of the genetic and environmental risk factors and their interactions increasing the susceptibility of T2DM, in the Portuguese population.

Methods: Case-control study with 1337 individuals, 467 diabetes and 1113 controls not significantly different in terms of age and gender. We investigated the variants, TCF7L2 C/T (rs7903146), FTO C/A (rs9900339) and HNF4A G/C (rs1884814). T student or chi2 tests with the OR and 95% CI, were used as indicated. Afterwards, multivariate analyzes and a 4x2 table approach, as well as synergy measurements in additive (Si) and multiplicative (SIM) models were used.

Results: The TCF7L2 TT genotype was more incident among diabetics (16.7%) vs. controls (11.0%) with an OR= 1.63 (1.28-2.24) p=0.002 and FTO AA was more in diabetic (16.8%) vs. controls (15.7%), but without statistical significance. There was no association with the HNF4A variant.

Conclusion: Our study provides the first significant evidence that the TCF7L2 TT polymorphism is a strong independent risk factor for T2DM in a Portuguese population. The subjects carrier of this variant must have early primary prevention for tackling these risk factors.
Predictors of long-term cardiovascular outcomes in patients with type 2 diabetes mellitus

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Introduction: Type 2 Diabetes mellitus (T2DM) is a public health problem associated with various risk factors such as hypertension, dyslipidemia and obesity. Prevalence of cardiovascular events in T2DM is twice the observed in non-diabetic subjects, even after adjustment for classic risk factors. Early detection of predictors of hard outcomes are needed to try to avert this scenario. Objectives: To identify biomarkers associated with higher rates of clinically relevant events in a prospective cohort of patients with T2DM.

Materials and Methods: A total of 1167 individuals were evaluated in a cohort of 323 individuals with T2DM followed by 10 years. Blood samples were collected at baseline. We examined biomarkers with potential risk of events in this population. Troponin, homocysteine, creatinine, fasting glucose, high-sensitivity C-reactive protein (CRP), and lipid profile were evaluated. Fatal and nonfatal acute coronary syndromes and stroke were evaluated. ECG and clinical information were obtained from all patients. Cumulative survival curves were analyzed by Log-rank/Mantel-Cox.

Results: The study population comprises individuals of both genders, 59% males, age 59y, with mean time of diagnosis of 8y, obese (39%), mostly with hypertension and dyslipidemia. The presence of prior myocardial infarction (MI) or angina (68%) was in 32% (Mean levels of CRP (µg/L) were 4.14 mg/dl. Sub analyses 0.015 ng/dl, homocysteine 10.86 umol/L, creatinine 0.89 mg/dl and estimated glomerular filtration rate (GFR) (Cockatoo-Gault) was 105.60 ml/min. Left ventricular hypertrophy (LVH, Perugia score) was present in 28% of patients. There were associations between higher event rates in males (HR 2.5 1.6-4.1), 24h MI (HR 1.4 1.4-1.6), decreased creatinine clearance (HR 1.6 1.1 to 2.5) and elevated levels of serum creatinine (>1.3 mg/dl for men and >0.8 mg/dl for women) (HR 2.3 1.1 to 4.3).

Conclusion: Male gender, previous MI and renal function impairment were associated with higher rates of cardiovascular events, thus highlighting the importance of risk factors and comorbidities in this high-risk population.

The association of the A3872G polymorphism with hs-c-reactive protein levels and peripheral arterial disease in patients with type 2 diabetes mellitus

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Purpose: The aim of this study was to examine the impact of A3872G polymorphism on C-reactive protein (CRP) gene on high sensitivity CRP (hs-CRP) levels and peripheral arterial disease (PAD) in patients with type 2 diabetes mellitus (T2DM). Methods: The study population consisted of 431 patients with T2DM (documented for PAD or not). The A3872G polymorphism was detected by polymerase chain reaction and appropriate restriction enzyme digestion (HpCh481I). Carotid intima-media thickness was assessed by particle-enhanced immunonephelometry. Peripheral arterial disease was evaluated based on history of intermittent claudication, reduced or absent foot pulses, interventional procedure of revascularization or amputation in case of severe claudication. hs-CRP levels were determined by nephelometry or by immunosorbent assay in lower leg arteries or ankle brachial pressure index (ABPI).<ref> Results: The genotype distribution was 52, 27.2, 20.8 for the GG, AG, AA genotypes respectively. [mean age 68.55 ± 19.93, males n=218 (50.6), females n=212 (49.2)] with significant gender difference males/females GG (46.4% vs15.6%), AG (50% vs50%), AA (61.8% vs38.2%; p=0.019). Hs-CRP levels were higher in GG homozygotes (GG: 0.61 ± 0.257) compared with carriers of ‘A’ allele (AG+AA: 0.56 ± 0.188; p=0.021). The presence/absence of PAD was not significantly different among the GG (34.2% vs38.5%), the AG (39.7% vs38.3%) or the AA (40.4% vs57.3%) genotypes (p=0.059). However, carriers of an ‘A’ allele (AG+AA) compared with GG homozygotes (GG) had increased odds (odds ratio (OR)=1.622, 95% confidence intervals 1.029-2.536, p=0.037, to have PAD after adjusting for gender, age, duration of diabetes, body mass index, smoking, hyperlipidemia, isolated systolic hypertension, albuminuria and use of angiotensin receptor blockers (lower odds for PAD for all). Conclusions: The CRP3872G polymorphism affects the hs-CRP levels and the presence of PAD in patients with T2DM. Specifically, the carriers of the ‘A’ allele although have lower levels of hs-CRP; they have higher odds for PAD than GG homozygotes. In addition, the odds for PAD are affected significantly by interactions between the carriers of the ‘A’ allele with other micro and macrovascular complications and the use of antiplatelet treatment. The CRP3872G polymorphism affects the hs-CRP levels and the presence of PAD in patients with T2DM. Specifically, the carriers of the ‘A’ allele although have lower levels of hs-CRP; they have higher odds for PAD than GG homozygotes. In addition, the odds for PAD are affected significantly by interactions between the carriers of the ‘A’ allele with other micro and macrovascular complications and the use of antiplatelet treatment. The CRP3872G polymorphism affects the hs-CRP levels and the presence of PAD in patients with T2DM. Specifically, the carriers of the ‘A’ allele although have lower levels of hs-CRP; they have higher odds for PAD than GG homozygotes. In addition, the odds for PAD are affected significantly by interactions between the carriers of the ‘A’ allele with other micro and macrovascular complications and the use of antiplatelet treatment. The CRP3872G polymorphism affects the hs-CRP levels and the presence of PAD in patients with T2DM. Specifically, the carriers of the ‘A’ allele although have lower levels of hs-CRP; they have higher odds for PAD than GG homozygotes. In addition, the odds for PAD are affected significantly by interactions between the carriers of the ‘A’ allele with other micro and macrovascular complications and the use of antiplatelet treatment. The CRP3872G polymorphism affects the hs-CRP levels and the presence of PAD in patients with T2DM. Specifically, the carriers of the ‘A’ allele although have lower levels of hs-CRP; they have higher odds for PAD than GG homozygotes. In addition, the odds for PAD are affected significantly by interactions between the carriers of the ‘A’ allele with other micro and macrovascular complications and the use of antiplatelet treatment.

One-third of patients with diabetes mellitus do not have subclinical coronary atherosclerosis

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Purpose: All patients with diabetes mellitus (DM) are recommended lipid lowering treatment, although not all are at similar risk. Measuring coronary artery calcification (CAC) enables to stratify further the cardiovascular risk, also in diabetics. The prevalence of CAC among random selected patients with DM is uncertain. For this purpose we set out to examine the occurrence of CAC in patients with DM, and compared it with non-diabetic subjects.

Method: A random selected cohort of 1825 men and women, 50 or 60 years old were invited to the screening study. DM was defined as the use of anti-diabetic medication or fasting plasma blood glucose level >7.0 mmol/l on two different days. Traditional risk factors were obtained and for the non-diabetics HeartScore was calculated. A non-contrast CT-scan was performed to assess the CAC score (Agatson score ≥400 was considered as high).

Results: A total of 1226 subjects without previous cardiovascular disease participated. Five % (59 subjects) had DM while 92% (1167 subjects) were non-diabetics. Among patients with DM the prevalence of males, 60 years old, smokers, hypertension and statin treatment were 45%, 58%, 32%, 57% and 55% respectively, while 47%, 50%, 25%, 49% and 10% for the non-diabetics. Also CAC was more frequent in diabetics (63% versus 44%; p=0.006), as well as severe calcification (9% versus 5%; p=0.02). Here we adjusted for covariates in multivariate logistic regression results only in a non-significant increased risk for calcification in diabetic patients (OR=1.3; p=0.44).

Conclusion: We found that one-third of patients with DM did not have any coronary calcification and thus a better prognosis, while few had severely calcified coronaries. These data suggest that also in diabetics preventive therapy should be individualised based on CAC.
Arterial elastic wall properties are similarly impaired in first degree relatives and diabetic patients on the grounds of significant insulin resistance

Methods: In 60 subjects without known diabetes a standard 75-g OGTT was performed and plasma glucose and serum insulin levels were measured at 0, 30, 60, 90 and 120 min after glucose loading. At the same time intervals we measured the carotid-femoral pulse wave velocity (PWVc) using the Complior apparatus and aortic PWV (PWVc) and augmentation index (AI) using an oscilometric method (Artiograph). We measured insulin resistance after fasting, using homeostatic model assessment (HOMA) and hepatic insulin sensitivity (HIS) b during OGTT using 45 days of LDLc measurement, and INS.

Results: Of the 60 subjects, 20 who were first degree relatives of diabetics had normal OGTT (relatives), 20 had normal OGTT and no family history of diabetes (normals), and 20 had abnormal OGTT (diabetics). Compared to normals, diabetics and relatives had both higher baseline PWVc (PWVc 10.4±2.6 vs, 9.1±1.3 m/sec, p <0.05), PWVc (9.1±2 vs. 8.9±2, 7.3±1.6±6 m/sec, p=0.05), AI (24.5±9 vs. 24.2±14, 21.8±155, p<0.05), insulin (14.6±15 vs. 14.6±15, 9.9±15, p<0.05), HOMA, (3.9±2.1 vs. 3.6±1.6 vs. 2.4±1.0, p<0.05) and lower HIS (0.32±0.24 vs. 0.33±0.24 vs. 0.48±0.18, 0.5±0.05), ISI (50±24 vs. 73±22 93±17, 0.5±0.05). Mat-suda index (3.1±1.6 vs. 3.0±1.6 vs. 3.3±1.2, p<0.05). Age, sex and BMI were similar in both groups. The differences observed were related to baseline AI was reduced at 30 min by 30% in normals and relatives (p>0.01) but only 6% in diabetics (p>0.5). Compared to baseline, insulin was increased at 30 min, to 54±1.6 μU/ml (484% in normals, p<0.001) and in diabetics 110±1.6 μU/ml (81% in relatives (p>0.01). The decrease in AI at 30 min was related to the corresponding % increase in insulin levels (n=46, p<0.05).

Conclusions: First degree relatives and diabetic patients have increased arterial stiffness and abnormal wave reflection compared to normals with no family history of diabetes. Normals and relatives show an acute decrease in AI related to the corresponding increase in insulin level likely because of insulin stimulation of endothelial cell nitric oxide synthesis. However relatives succeed this effect by raising their insulin levels nearly twice as those of normals suggesting the onset of insulin resistance as confirmed by estimated indices of insulin resistance. In diabetics the effect of insulin on AI is blunted likely because of severe insulin resistance.

Suboptimal LDL cholesterol control by atorvastatin monotherapy in high-risk patients with coronary heart disease or atherosclerotic vascular disease in the UK

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Purpose: Presence of coronary heart disease (CHD) or atherosclerotic vascular disease (AVD) places a patient at high risk for a cardiovascular (CV) event. Lowering LDL cholesterol (LDL-C) is associated with proven clinical benefit and was proved to be primary predictor of vascular events in high-risk patients. LDL-C goals recommended by European guidelines are dependent upon pre-existing CV risk factors. Since statins are widely recommended and approval of generic atorvastatin (ATORVA) will increase its use, this analysis examined LDL-C goal attainment in high-risk patients treated with ATORVA monotherapy.

Methods: Using a UK general practice database, patients who received a prescription for ATORVA monotherapy (the index Rx) between 01/01/08 and 11/30/10 were identified. Additional inclusion criteria were: an ICD-10 diagnosis of CHD or AVD, <1 LDL-C measurement between 3 mo and 1 yr post index Rx, an ATORVA Rx in the index Rx, LDL-C measurement at index Rx and <6 months prior to index Rx. Endpoints were the proportion of patients achieving an LDL-C <1.8 mmol/L (very high-risk goal in 2011 ESC guidelines), <2.0 mmol/L (high-risk goal and 2007 ESC guidelines), or <2.5 mmol/L (optional goal).

Results: Of 2,403 high-risk patients (65% males, mean age 69 yrs [SD 10]) who met selection criteria, 24, 27, 35, and 14% received Rx for 10-, 20-, 40-, and 80-mg dose of ATORVA, respectively. 24% of patients were initiated on ATORVA monotherapy at the index date. Mean follow-up LDL-C was 2.14 mmol/L (SD 0.68). Overall, 27% of patients had an LDL-C <1.8 mmol/L, 41% had an LDL-C <2.0 mmol/L, and 75% had an LDL-C <2.5 mmol/L. Greater goal attainment was observed with the highest ATORVA dose (Table 1).

Conclusions: In UK patients at high CV risk, LDL-C goal attainment with ATORVA monotherapy was suboptimal, with over 60% not achieving an LDL-C <1.8 mmol/L even at the highest dose. This suggests that more effective lipid-lowering strategies such as, more aggressive dose titration or add-on therapy, are required to achieve LDL-C goals in these patients.

Type 2 diabetes and the progression of visualized atherosclerosis to clinical cardiovascular events

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Purpose: We aimed at prospectively evaluating to what extent pre-existing coronary artery disease (CAD) accounts for the increased long-term vascular event risk of patients with type 2 diabetes (T2DM). Methods: Vascular events were recorded over 8 years in 750 consecutive patients whose baseline CAD state was verified angiographically.

Results: The baseline prevalence of CAD (87.8% vs. 80.4%, p<0.029) and of significant coronary stenoses (50.95% vs. 58.4%, p<0.001) as well as the extent of CAD, defined as the number of significant coronary stenoses (1.7±1.6 vs. 1.4±1.5, p=0.014) were higher in patients with T2DM (n=164) than in non-diabetic subjects. During follow-up, T2DM and CAD proved to be mutually independent predictors of vascular events: T2DM predicted vascular events (n=257) independently from the presence and extent of baseline CAD (hazard ratio [HR] 1.36 [1.09–1.70], p=0.02). However, the overall risk increase driven by T2DM was driven by an extremely high 53.3% event rate (90.7±1.5 mmHg, diastolic blood pressure: 76.9±3.3 mmHg, fasting plasma glucose: 4.8±1.0 mmol/l, fasting insulin: 7.9±1.0 mlU/ml, HOMA-A: 1.7±0.2; mean±SD) were not equal to the study. Transthoracal echocardiography was used for the determination of arterial elasticity. It was characterized by aortic distensibility (AD), aortic stiffness index (ASI) and aortic strain (AS) which were calculated using aortic ascending dimensions (systolic and diastolic diameters) measured during transthoracal echocardiography and blood pressure. The relationships between parameters were analysed by linear regression model. Statistical analysis was performed by SPSS program.

Results: There were statistically significant negative correlations between HOMA-A and AD (r=−0.689, p=0.001) and AS (r=−0.663, p=0.001). The correlation between HOMA-A and ASI (r=−0.770, p=0.00005) was positive. The results were similar between fasting insulin level and relevant aortic parameters (AD: r=−0.705, p=0.0004; AS: r=−0.663, p=0.001; ASI: r=0.723, p=0.0002). There was no significant correlation between the fasting plasma glucose and aortic elasticity.

Conclusions: Our results revealed a close relationship between decreased insulin sensitivity within the normal range and aortic stiffness in healthy subjects which may forecast the early cardiovascular adaptation damage.
Preliminary observations of passive exercise using whole body periodic acceleration (WBPA) system is currently developed as a passive exercise device by providing increased pulsatile shear stress for improvement of peripheral and coronary endothelial function (Figure left). This study aimed to investigate the acute effects of WBPA on coronary microcirculation and glucose tolerance in patients with type 2 diabetes (T2D).

Methods: The study subjects were 8 patients with T2D who underwent transthoracic Doppler echocardiography (TTEC) for the assessment of coronary flow reserve (CFR) before and immediately after 45-min session of WBPA. The flow velocity in the distal portion of the left anterior descending coronary artery was measured at baseline and during adenosine infusion. The CFR represented the ratio of hyperemic to basal mean diastolic flow velocity.

Results: WBPA was completed and well-tolerated in all patients, and no significant hemodynamic or mechanical complications were observed during the procedure or follow-up. WBPA increased CFR from 2.3±0.3 to 2.6±0.4 (p=0.02) (Figure right). WBPA decreased serum insulin level from 26.1±19.9 μU/ml to 19.1±15 μU/ml (p<0.01) and increased total adiponectin from 116±73 μg/ml to 125±80 μg/ml (p<0.02). No significant differences in high molecular weight adiponectin from 4.9±3.6 μg/ml to 5.3±3.9 μg/ml (p=0.03), whereas the serum glucose level was stable from 207±66 mg/dl to 203±56 mg/dl (p=0.8).

Conclusions: This study demonstrates that a single session of WBPA treatment simultaneously improved coronary microcirculation and glucose tolerance in patients with T2D, providing the mechanical insights into the relationship between exercise and adiponectin.

Predictors of Hypoglycaemia in patients with Type-2 Diabetes - an Analysis of the Prospective DiaRegis Registry

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Hypoglycaemia is a serious complication of antidiabetic drug therapy, especially when treatment is intensified. We aimed to identify predictors of hypoglycaemia in a cohort of type-2 diabetic patients prospectively followed over a one year follow-up. Using logistic regression analysis with stepwise backward selection (alpha 0.05) independent predictors of hypoglycaemia were determined. A total of 3347 patients were available for the present analysis. Of these 473 (14.1%) had hypoglycaemia of any severity over a follow-up of 12 months. Patient with incident hypoglycaemia had a longer diabetes duration, a higher HbA1c and more frequent co-morbid disease conditions such as coronary artery disease (CAD), peripheral arterial disease (PAD), amputation, heart failure, peripheral neuropathy, diabetic retinopathy and clinically relevant depression at baseline. Multivariable adjusted positive predictors of incident hypoglycaemia over the 12 months follow-up were prior anamnestic hypoglycaemia (OR 4.50), retinopathy (OR 3.27), clinically relevant depression (OR 1.81) and insulin use (OR 2.99). On the contrary, glitazones (OR 0.55), DPP-4 inhibitors (OR 0.57) and GLP-1 analogues (OR 0.48) were associated with a reduced risk of hypoglycaemia. Incident vascular disease such as stroke/transitory ischemic attack, amputation, autonomous neuropathy, non-proliferative retinopathy and also clinically relevant depression were more frequent in those patients reporting hypoglycaemia during follow-up than in those without this complication. We conclude that hypoglycaemia is a frequent complication in ambulatory patients when treatment is intensified. Particular attention is warranted in patients with prior episodes of hypoglycaemia, microvascular disease such as retinopathy and in patients receiving insulin. On the other hand glitazones, DPP-4 inhibitors and GLP-1 analogues appear to be associated with a reduced risk.

Blood pressure response to exercise is exaggerated in normotensive diabetic patients

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Objective: The aim of this study was to investigate the blood pressure (BP) response to exercise in normotensive patients with type II diabetes mellitus (DM). Methods: A cross-sectional study was carried out on 75 normotensive subjects with type 2 DM (Group 1), and 70 age-gender matched normotensive healthy volunteers (Group 2). Treadmill exercise test, 24 hours ambulatory BP monitoring (ABPM) were performed for each patients and healthy volunteers. Results: There were 67 patients (mean age 52±9 and 42% male) in group 1 and 68 healthy volunteers (mean age 51±7 and 43% male) in group 2. Eight patients from group 1 and 2 subjects from group 2 were excluded because of high
Serum adiponectin is a negative predictor of incident metabolic syndrome: a population-based follow-up study

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Objective: Growing evidence suggests that increased adiponectin levels may play an important role in the development of metabolic abnormalities, but prospective studies of adiponectin levels and incident metabolic syndrome are lacking. We investigated whether serum adiponectin predicts incident metabolic syndrome and its components in a population-based longitudinal study.

Methods: We analyzed data from 2,068 adults (838 men and 1,230 women) without metabolic syndrome, aged 40 to 70 years, who participated in a health survey in 2006. Baseline serum adiponectin concentrations were measured by radioimmunoassay. Metabolic syndrome was defined according to the modified National Cholesterol Education Program Adult Treatment Panel III report.

Results: During an average of 2.6 years of follow-up, 154 men (16.4%) and 206 women (16.8%) developed metabolic syndrome. Median baseline adiponectin levels in subjects who developed metabolic syndrome were significantly lower than those who did not, both in men (7.09 vs. 8.63 μg/mL, p < 0.001) and women (10.96 vs. 12.16 μg/mL, p < 0.001). In multivariable adjusted models, the odds ratio (95% confidence interval) for incident metabolic syndrome comparing the highest to the lowest quartiles of adiponectin levels was 0.26 (0.14 – 0.48) in men and 0.27 (0.13 – 0.54) in women. Serum adiponectin levels were also associated with the number of metabolic syndrome components developed by study participants over follow-up (P trend < 0.001 in both men and women).

Conclusion: Our findings suggest that increased serum adiponectin could be a negative predictor of incident MetS and its components.

TAKING INTO ACCOUNT THE ECONOMIC CRISIS IN CARDIOLOGY

Cost-effectiveness of cardiac resynchronization therapy in combination with an implantable cardioverter defibrillator in mild heart failure based on a Markov model using UK cost approach in MADIT-CRT

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Aim: To evaluate the cost-effectiveness of CRT-D in mild heart failure LBBB or female patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (MADIT-CRT).

Methods: A decision analytic Markov model was created to evaluate the costs, gained life-years and quality-adjusted life years (QALYs) associated with CRT-D compared to ICD treatment. Analysis was performed in 1,281 LBBB patients and in 453 CRT-females enrolled in MADIT-CRT from the perspective of the United Kingdom National Health Service. Costs and utilities were discounted at 3.5% per year. Base-case analysis and multiple one-way sensitivity analyses were performed.

Results: Compared with ICD treatment, CRT-D gained 1.51 QALYs having a cost of £19,855 in LBBB patients, resulting in an incremental cost-effectiveness ratio (ICER) of £13.147 per QALY gained when using a lifetime horizon of 35 years. The female population gained 3.81 QALYs at an additional cost of £30.088 respectively. One-way sensitivity analyses revealed the discount rate and the utility per cycle without heart failure events to be the most sensitive variables for cost-effectiveness. Conclusions: CRT-D treatment is cost-effective in mild heart failure LBBB or female patients with severely decompensated heart failure and a wide QRS when compared to ICD only, for a 10-year and 35-year time horizon.

Cost-effectiveness of the molecular autopsy in sudden unexplained death in the young

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Purpose: Sudden unexplained death (SUD) accounts for 30% of young sudden cardiac deaths under the age of 35 years. The underlying cause is suspected primary arrhythmogenic disease in such cases, including long QT syndrome (LQTS). The “molecular autopsy” (genetic testing of postmortem DNA) can clarify both the cause of death, and the genetic status of asymptomatic family members. This study sought to determine the incremental cost-effectiveness of a family management strategy including the “molecular autopsy” in addition to conventional clinical screening, compared to clinical screening alone.

Non-dipping heart rate and microalbuminuria in a type 2 diabetic population

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Purpose: There is increasing interest in the association between non-dipping heart rate and target organ damage. However, this has not been adequately studied in diabetic patients. The aim of the study is to identify factors that are independent predictors of non-dipping heart rate in a type 2 diabetic population who is at high risk of cardiovascular disease.

Methods: One hundred eighty six type 2 diabetic subjects with mean diabetes duration of 18.3 (± 9.5) years were recruited. All participants had proliferative retinopathy, thus enabling analysis of factors independent of glycaemic control. All underwent 24-hour BP and heart rate monitoring, and were assessed for markers of inflammation (erythrocyte sedimentation rate and high-sensitivity C-reactive protein), insulin resistance as well as albuminuria, presence of peripheral neuropathy (as assessed using vibration perception thresholds) and peripheral vascular disease. Data were analysed using SPSS version 20.0.

Conclusion: The non-dipping heart rate did not decrease > 10% as compared to day-time readings were classified as non-dippers. Independent samples t-test and Mann-Whitney U test were performed for parametric and non-parametric variables respectively, while categorical variables were analysed using chi-squared test. Multivariate regression analysis ensued to identify independent predictors of non-dipping heart rate. A logarithmic transformation was performed when variables were not normally distributed.

Results: Univariate analysis revealed that non-dippers had significantly higher logarithmic albumin-creatinine ratio (ACR) (p<0.001) and higher platelet count (p<0.014). Also, non-dippers were more likely to be on β-blockers (p<0.037). There was no difference between dippers and non-dippers as regards age, glycaemic control, diabetes duration, markers of inflammation, insulin resistance as well as well as platelet count (p<0.026) were independent predictors of non-dipping heart rate, even when correcting for β-blocker use.

Conclusions: In this high risk type 2 diabetic population with diabetes of long duration, non-dipping heart rate was independently associated with ACR and platelet count. Non-dipping heart rate might give us an indication of underlying generalized atherosclerosis in diabetic patients. This merits further study.
Methods: A decision model was constructed to depict the two strategies: (i) clinical screening including the "molecular autopsy" and (ii) the conventional approach of clinical screening alone. Input data were based on published research where available and expert opinion (Table 1). Costs were from a third-party payer perspective, and presented in Australian dollars ($A = £0.808). Effectiveness was measured using life-years gained (LYG). One-way sensitivity analysis was carried out to assess the impact of each input variable on the overall incremental cost-effectiveness ratio (ICER).

Results: Assuming a 35% mutation pick-up rate (cost $A35000/2829 to screen 4 genes) and 1.5% (HERG, SCN5A, RyR2) and 4 family members per decedent, the addition of the "molecular autopsy" to conventional family management was found to be cost-saving, dominating the clinical screening strategy. One-way sensitivity analysis found the key variables to be the cost of the "molecular autopsy" and the mutation detection rate. If the cost of genetic testing was more than $A3988 (£3224), or the mutation detection rate below 28% then it became the least cost-effective strategy.

Conclusions: The addition of the "molecular autopsy" to the conventional approach of clinical screening is a cost-saving strategy. There is significant cost-saving benefit in predictive genetic testing of the surviving family members, particularly for those who test gene negative. The "molecular autopsy" is expected to become even more cost saving as newer genetic technologies facilitate testing more genes, at lower cost, with higher mutation detection rates.
Conclusions: There is a positive, significant change in the guidelines of the ESC towards the reduction of guidelines based on the expert opinion (Level C) and on divergence in opinion (Class II). Despite many randomized studies published in last years, still less than 25% of current recommendations is based on the strongest evidence (Level A) and an effort should continue to obtain a significant increase in this section.

A retrospective cohort of long term all-cause mortality and recurrent cardiovascular events in patients with acute coronary syndrome in Thailand

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Objective: To assess the long-term outcome of patients presenting with acute coronary syndrome (ACS); ST-segment elevation myocardial infarction (STEMI), non-STEMI and unstable angina (UA) in Thailand.

Methods: This is a retrospective cohort study. The data of admission and the vital status were obtained from the records of ICD 10 and ICD 9CM systems of central office for healthcare information and bureau of policy and strategy of Thailand. All patients admitted to the hospitals using 2 health security services of Thailand; national health security (UC) and civil servant (CS) due to ACS, in 2005 (from January 1st - December 31st) were collected and followed through 2010. Primary outcome was 5 years all-cause mortality.

Results: A total of 31,087 patients with ACS in 2005 were collected. In-hospital death rate was 14%. A total of 26,722 patients (86%) survived at discharge (UA 51.6%, MI 48.4%). The post-discharge overall all-cause mortality was 11.3% and 40.6% at 1 and 5 years, respectively. At 5 years, post-discharge all-cause mortality of patients presenting with MI was significantly higher than that of UA (43% vs 38.4%, HR 1.18; 95%CI 1.14-1.23, P<0.0001). Among the patients with MI, those with NSTEMI died after hospital discharge more than those with STEMI (48.7% vs 37.5%, HR 1.42; 95%CI 1.31-1.53, P<0.001). Despite in-hospital mortality was higher in STEMI. The composite endpoints of death or recurrent MI, death or stroke, death or heart failure were 15.4%, 11.7% and 17% at 1 year. Multivariate analysis of age, sex, diabetes, history of coronary artery disease, comorbid diseases (ischemic stroke, atrial fibrillation, heart failure, chronic kidney disease), history of in-hospital cardiac arrest showed all these factors were independent risk of death. Patients using CS security service died less than those using UC. Revascularization and CS security service were significantly independent protective factors of death (HR 0.58; 95%CI 0.54-0.63, P<0.0001 for revascularization and HR 0.83; 95%CI 0.79-0.86, P<0.0001 for CS security service).

Conclusion: The post-discharge all-cause mortality and subsequent morbidity burden of ACS in Thailand are still high when compared to other countries. These findings will be useful for the improvement of treatment and health systems in Thailand.

AMBULATORY BLOOD PRESSURE MONITORING: FOCUS ON NOCTURNAL BLOOD PRESSURE

Non-dipping pattern in untreated hypertensive patients is related to increased pulse wave velocity independent of raised nocturnal blood pressure

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Background: Non-dipper pattern, characterized by diminished nocturnal decline in blood pressure (BP), is associated with increased arterial stiffness. In this study, we investigated the association between pulse wave velocity as the surrogate of arterial stiffness and non-dipper pattern in untreated hypertensive patients.

Methods: Eighty-four hypertensive patients, consulted for initial evaluation of hypertension, were enrolled. CF-PWV as the indicator of arterial stiffness was measured by a validated tonometry system (Sphygmocor). Patients with the history of any cardiovascular disease were excluded from study.

Results: The thrombocyte serotonin level was 378.9±95.1 pg/ml and the serum uric acid was 6.6±1.1 mg/dl. The thrombocyte serotonin level was higher in non-dippers (P<0.001). Multiple logistic regression analysis including age, gender, BP and PWV measurements, revealed female gender (OR: 5.112; 95%CI: 1.292-20.4, P=0.021), nocturnal mean BP (OR: 1.243; 95%CI: 1.107-1.396, P<0.001) and CF-PWV (OR: 1.992; 95%CI: 1.240-3.198, P=0.004) as the independent predictors of non-dipper hypertensive pattern.

Conclusion: Our findings indicate that even though ambulatory blood pressure monitoring induces modest sleep disturbances, it can accurately evaluate night-time blood pressure profile and heart rate, without affecting sleep efficiency and quality. Sleep evaluation may be particularly useful in essential hypertension, as poor quality of nocturnal sleep was associated with non-dipping status.
Circadian variation of blood Pressure is impaired in normotensive pregnant women with gestational diabetes mellitus

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Purpose: Approximately 5% of all pregnancies are complicated by gestational diabetes mellitus (GDM). Gestational diabetes mellitus is accepted as a risk factor for long-term metabolic dysfunction of pregnancy, prolonged insulin resistance and associated with elevated risk of gestational hypertension. Since GDM is a state of temporary insulin resistance, in this context we therefore aimed to test our hypothesis that day time circadian blood pressure variation is impaired even in normotensive women with GDM. We sought to determine this hypothesis by comparing the normotensive women complicated with GDM with normal pregnant women in terms of holter monitoring derived dipper and non-dipper circadian variation of blood pressure profile.

Methods: Forty-two women with GDM and 33 normal uncomplicated pregnant subjects were screened and diagnosed between 24 and 28 weeks of gestation, according to the criteria of the American College of Obstetricians and Gynecologists. Twenty-four hour non-invasive ambulatory blood pressure monitoring by using a portable compact digital recorder (Suntech SP-100) was carried out on a weekday. In order to obtain diurnal an nocturnal values, diurnal_readings at 20-min intervals and nocturnal readings at 30-min intervals were recorded. Nocturnal blood pressure dipping was calculated as follows: (Awake BP – Sleep BP) x(100/Awake BP). Patients with a nocturnal reduction in average daytime systolic BP and diastolic BP of less than 10% were classified as nondippers, while those with nighttime reduction of 10% or more were classified as dippers. All patients underwent echocardiographic examination to determine left ventricle mass index and diastolic dysfunction.

Results: Left ventricle mass index was significantly higher in GDM group (179.9±14.2 g/m² vs 155.9±15.6 g/m², p=0.004). Diastolic dysfunction parameters including mitral E and velocities, deceleration time, isovolumetric relaxation time were in favor to diastolic dysfunction in GDM group (p=0.019, p=0.03, p=0.001, respectively). Night phase systolic blood pressure and night phase diastolic blood pressure were higher in GDM group (111.16±7.5 vs -7.5; p<0.001 and 69.6±9.4 vs 66.0±5.1, p=0.001, respectively). Nocturnal systolic and diastolic blood pressure dipping were diminished in GDM group (-4.06±3.7 vs -8.92±3.6, p<0.001 and -6.95±5.1 vs -8.6±5.4; p=0.001, respectively). Serotonin level was negatively correlated with blood pressure dipping (r=0.01, p<0.01). Nocturnal systolic SBP was significantly more prevalent among non-dippers compared to dippers (78% vs 23%, p<0.05).

Conclusion: In non-dipper hypertensive patients, thrombocyte serotonin levels and CRP (p<0.001) were recorded and venous blood samples were drawn for estimation of high sensitivity C-reactive protein (hs-CRP) and homocysteine levels. Self-reported data were recorded and venous blood samples were drawn for estimation of high sensitivity C-reactive protein (hs-CRP) and homocysteine levels. Self-reported data

Conclusions: We have showed that clinically diagnosed RLS was associated with the nondipping pattern which was shown to be a predictor of cardiovascular risk.

Dipping status is characterized by augmented administration of benzodiazepines and elevated arterial stiffness

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Purpose: Blunted reduction of blood pressure (BP) fall as well as psychologi- cal stress have both been related to adverse cardiovascular prognosis and po- tentially to neuroplasticity as a common pathophysiological substrate. We hypothesised that dipping status might be correlated with benzodiazepine's administration (sympatholytic action) in the setting of essential hypertension. Restless legs syndrome was assessed by a self-administered questionnaire based on the International Restless Legs Study Group criteria.

Methods: This cross-sectional study included 230 consecutive patients with never-treated hypertension who presented to our institution for initial evaluation of ambulatory blood pressure monitoring: focus on nocturnal blood pressure 899

Results: The study group, 133 patients were diagnosed as hypertensive (53.4% nondippings) and 81 patients as normotensive (54.3% nondippings). The prevalence of RLS, globally, were significantly higher in nondippings compared with dippings (34.7% vs 21.2%, respectively; p<0.028). Logistic regression analysis showed that the RLS is an independent determinant for both hypertension (odds ratio=0.43 [95% confidence interval (CI)=0.21–0.83; P<0.013) and the nondipping blood pressure patterns (odds ratio=1.96 [95% confidence interval (CI)=1.05–3.67, P<0.05]).

Table 1. Independent predictors of nondipping blood pressure profile

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.97</td>
<td>0.89–1.05</td>
<td>0.002</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.999</td>
<td>0.541–1.846</td>
<td>0.999</td>
</tr>
<tr>
<td>BMI</td>
<td>1.555</td>
<td>0.812–2.978</td>
<td>0.194</td>
</tr>
<tr>
<td>RLS</td>
<td>1.965</td>
<td>1.050–3.678</td>
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</tbody>
</table>

Conclusions: In conclusion, non-dippers compared to dippers hypertensives were more characterized by increased benzodiazepine's administration, impaired arterial elasticity and more pronounced activation of prothrombotic mechanisms.

Inverse dose-response association between urinary melatonin excretion and nocturnal systolic blood pressure in the elderly

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Purpose: Oral melatonin administration decreases nocturnal systolic blood pressure (SBP); however, it remains unclear whether endogenous melatonin, consider- ably lower than pharmacological levels, is associated with nocturnal SBP. The purpose of this study was to evaluate the association between urinary melatonin excretion (UME), an index of endogenous melatonin, and nocturnal SBP.

Methods: In this cross-sectional study, 109 elderly individuals aged 60 years or older (50 males, 69.1±6.1 years), not taking antihypertensive medication, and completed two 48-h monitoring sessions were consecutively selected from 217 subjects. We simultaneously measured overnight UME (6-sulfatoxymelatonin), ambulatory SBP at 30-min intervals, and physical activity evaluated by actigraphy. The final model was based on 216 BP data (the average in 48 h) from 109 participants.

Results: The median UME was 7.6 μg (interquartile range 4.7–11.5) and mean nocturnal SBP was 114.8±17.8 mmHg. Univariate mixed linear regression analysis showed significant associations between nocturnal SBP and age, gender, current smoking status, diabetes, log-transformed UME, daytime physical activity,
nocturia, and duration in bed. In a multivariate mixed model controlling simulta-
necessarily for the former confounders, log-transformed UME was significantly asso-
ciated with nocturnal SBP (regression coefficient: −3.6, 95% confidence intervals [CI] from −7.0 to 0.1, p=0.042). Moreover, to explain this association more prac-
tically, nocturnal SBP was estimated to decrease by 3.2 mmHg (95% CI from 0.1 to 6.4 mmHg) when UME increased from 4.7 μg (1st quartile value) to 11.5 μg (3rd quartile value; Figure).

Figure 1. Estimated effect of UME on nocturnal SBP

Conclusion: An inverse dose–response association exists observed between UME and nocturnal SBP among elderly individuals.

P5025

Characterization of isolated nocturnal hypertension in adolescents

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Objective: To determine the prevalence and characteristics of isolated nocturnal hypertension (INH) in adolescents from Maracaibo, Venezuela.

Methods: It was conducted a prospective and transversal study that included 621 subjects, 264 males and 357 females, mean-age: 14.6±1.7 years, who were underwent 24-h ambulatory blood pressure (BP) monitoring (ABPM) to obtain BP during awake and sleep periods. The presence of INH was defined as sleep BP higher or equal than 95th percentile and awake BP less than 95th for age and gender. Demographic (age, gender), anthropometric data [weight, height, waist circumference (WC) and hip circumference (HC)] and office blood pressure were registered. Also, serum glucose, lipids, fibrinogen and insulin, as well as C-reactive protein (CRP) were determined. The prevalence of INH and its 95% confidence intervals (95% CI) was calculated in all adolescents and by gender. The ANOVA test was used to study the effects of all factors included in the study on the INH.

Results: The INH prevalence was 15.8% [n=98; 95% CI: 12.9–18.7%] in all subjects, 15.5% [n=41; 95% CI: 11.1–19.9%] in males and 16.0% [n=57; 95% CI: 12.2–
19.8%] in females (p < NS). Adolescents with INH showed significant higher values than normotensives in the following factors: weight (60.7±16 vs. 54.8±13 kg, p=0.0001), height (161.7±9 vs. 159.7±10 cm, p=0.0001), WC (75.1±12 vs. 71.0±10 cm, p=0.0001), HC (93.2±10 vs. 89.3±9 cm, p=0.0001), office BP (132.4±19/82.4±19 vs. 102.9±11/58.6±6 mmHg, p<0.0001) and triglycerides (89.5±44 vs. 77.7±36 mg/dl, p=0.0001). Age and gender did not show statisti-
cally significant effects on INH.

Conclusions: There is a very high INH prevalence in adolescents. In this age group, the anthropometric measures are important factors to be evaluated in order to establish the presence of INH. This condition is extremely important because it is associated with significant cardiovascular abnormalities associated with INH.

AMBULATORY BLOOD PRESSURE MONITORING AND TARGET ORGAN DAMAGE

P5027

Does blood pressure variability influence the left ventricle mass index in patients with primary arterial hypertension?

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Background: Arterial hypertension (HA) leads to left ventricular (LV) hypertro-
phy which is a potent independent risk factor. Blood pressure (BP) variability has shown a significant relationship to end organ damage. Ambulatory blood pressure monitoring (ABPM) allows to observe a BP variability as well as short-term (beat to beat) as long –term (diurnal variations). The aim of this study was to assess whether the BP variations influence the LV mass index (LVMI) in patients with primary HA.

Material and methods: 97 pts (45 women and 52 men) with primary HA, aged 60.1±10.9 years underwent 24-h ABPM and ECHO measurements. The LV mass was calculated using the Penn formula and the result was corrected to body sur-
face to obtain the LVMI. For the purpose of estimating the long-term variability of BP the dipping status was assessed. Additionally the following parameters of short-term variability of BP were determined:

– Standard deviation (SD) between values of the consecutive BP measurements.
– Rate of BP changes calculated separately for systolic BP (SBP) and diastolic BP (DBP) using the formula: [BPn – BP(n-1)] / 60.0, where BPn is the value of BP; 60.0, time of measurement, n; measurement; n+1, next measurement after measurement n.

Results: In the study group LVMI ranged from 114 to 289 g/m². There were 52 non-dippers (without nocturnal fall in BP), 27 dippers (with preserved circadian pattern of BP), and 18 reverse dippers (with nocturnal increase in BP). There were no differences in LVMI between dippers, non-dippers and reverse dippers. We also did not find any correlations between LVMI and SD. The rate of SBP changes (RSBP) ranged from −0.37 to 0.16 mmHg/min, the rate of DBP changes RDBP ranged from −0.7 to 0.12 mmHg/min. No correlation was found between RSBP or RDBP and LVMI. However, the significant correlations with LV mass index re-
vealed: 24-hour mean SBP and mean daily SBP (r=0.51 and r=0.53, p<0.0001), mean nocturnal SBP (r=0.41, p<0.001), 24-hour mean DBP and mean daily DBP (r=0.48 and r=0.49, p<0.0001), minimal SBP and DBP during the day (r=0.56 and r=0.48, p<0.0001), minimal nocturnal SBP and DBP (r=0.47 and r=0.49, p<0.001), max.SBP during the day and the night (r=0.35 and r=0.32, p<0.01), max.DBP during the day (r=0.41, p<0.001) and the night (r=0.46, p<0.01).

Conclusions: 1. There is lack of relationship between the dipping status or the short-time variation of BP and the magnitude of LV mass index in primary HA.

2. From among several parameters obtained during ABPM only values of BP presented the most significant correlation with the LV mass index.

Conclusion: 1. Asymptomatic newly diagnosed hypertensive subjects with Abn. BP rise PME have significantly higher CV functional/structural abnormalities regardless of sex, than those with normal BP rise PME; 2. Hence we propose that asymptomatic subjects with newly diagnosed HTN should be screened for evi-
dence of any functional/structural CV abnormalities; which will mandate more aggres-
vive therapeutic interventions
Combined effects of blood pressure and aldosterone on cardiac left ventricular mass - ethnic differences between Han, Kazakh and Uygur subjects

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Purpose: Hemodynamic factors such as blood pressure have been established to be major determinants of cardiac left ventricular structure. However, factors other than blood pressure have also been shown to influence cardiac mass. We performed a medical survey and found that cardiac left ventricular mass index (LVMI) in an ethnic group of China with higher blood pressure was smaller than in another ethnic group with lower blood pressure. Here, such contradictions were analyzed with regard to blood pressure, LVMI and chemical parameters of blood and urine.

Methods: In a medical survey conducted in Xinjiang, China, 303 subjects (age, 65-70 years) from 3 ethnic groups (Han, Kazakh and Uygur) from two separate regions provided blood and urine samples, and underwent a 24-hour ambulatory blood pressure monitoring (AB-PM). The Ethics Committee of Xinjiang Medical University approved all study protocols. All subjects provided informed consent prior to their participation in the study.

Results: Systolic and diastolic blood pressure obtained by AB-PM were significantly higher in the Kazakh than in Han and Uygur groups. However, LVMI in Kazak was lower than those in other 2 groups. Plasma aldosterone (PA) and plasma renin activity (PRA) were significantly lower in Kazakh. Values for LVMI in all ethnic groups were positively correlated with both blood pressure and PA. An inverse correlation was observed between PA and urinary sodium excretion value. Although highest blood pressure was seen in Kazakh subjects, LVMI was lower than those of Han and Uygur, who showed lower blood pressure. These results suggest that blood pressure is not always a determinant of LVMI value. It is possible that relatively low PA resulting from higher sodium intake suppressed the increase in LVMI caused by higher blood pressure in Kazakh subjects.

Diastolic but not systolic blood pressure was more significantly affected by the gender in newly diagnosed hypertensive patients with obesity

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1Chonnam National University Hospital, Gwangju, Korea, Republic of; 2Kwandong University, Cheon General Hospital, Seoul, Korea, Republic of; 3Koryoung University Hospital, Daejeon, Korea, Republic of; 4Yonsei University, Severance Hospital, Seoul, Korea, Republic of; 5Catholic University Hospital, Seoul, Korea, Republic of; 6Inha University Hospital, Inchon, Korea, Republic of; 7Samsung Medical Center, Cardiovascular Center, Seoul, Korea, Republic of

Background: Obesity is associated with an increased risk of cardiovascular morbidity and mortality as well as life quality. Body mass index (BMI) provided the most useful parameter of obesity. The aim of this study, we tried to search the differences in certain well-defined blood pressure pattern according to gender between obese and non-obese patients.

Methods: Total 773 hypertensive patients (442 male, 431.8±11 years) enrolled from Korean Hypertension Network II were evaluated in this study. The patients were no taking BP lowering therapy and BP was checked by nurse or doctor in office. Automated self measurement in home and ambulatory monitoring. The study population was divided into two groups based on their BMI (obese group ≤ 24kg/m2 and non-obese group I > 25kg/m2). The mean systolic and diastolic BP for both male and female categories of patients were compared between two groups. In female, there was no significant difference of systolic and diastolic BP measured in office, home and ambulatory monitoring between groups.

Results: In male gender, there was no significant BP difference was measured in office, home and ambulatory monitoring between groups. Mean diastolic BP in office (97.1±12 vs. 94.1±11mmHg, p=0.016), average diastolic BP in AM at home (92.1±14 vs. 86.1±11mmHg, p=0.02), average diastolic BP in PM at home (94.1±14 vs. 86.1±11mmHg, p=0.010) and mean diastolic BP in home (91.1±12 vs. 87.1±11mmHg, p=0.005) were significantly higher in obese group than non-obese group. There was significant difference in BP pattern between obese and non-obese group was obtained from ambulatory monitoring. Although there was no clinical significance.

Conclusions: Diastolic mean BP from all measurement included office, home and ambulatory monitoring in hypertensive patients.
Antihypertensive treatment less efficacious when evaluated by Ambulatory Blood Pressure Monitoring

V. Gini, G. Gini. Internal Medicine Clinic, Hospital of Fier, Albania

Ambulatory blood pressure monitoring (ABPM) is now widely used not only for a better diagnosis of hypertension, but also for considering of antihypertensive treatment.

Purpose: We aimed to study the efficacy of antihypertensive drug treatment by analyzing office and ABPM recorded values.

Methods: From a database of more than 1000 ABPM recordings we have selected 146 pts whose BP was monitored twice, first without and then 2 weeks after beginning of standard antihypertensive treatment. Office measured, peak and mean (systolic/diastolic) values were selected for comparison. Treatment was considered efficacious when BP values (either systolic or diastolic) were reduced ≥10 mm Hg, or when they were returned to normal (≤130/80 mm Hg).

Results: At first evaluation Office (sys/dia) BP values (mean±SD) were 145±18 and 96±14 mm Hg. Peak 171±20 and 113±15 mm Hg and Mean 136±14 mm Hg, 83±10 mm Hg, respectively. After a 2-week treatment the Office BP values were significantly reduced to 138±16 (p<0.001) and 91±11 mm Hg (p<0.001), Peak BP values to 167±19 (p<0.001) and 107±15 (p<0.001) mm Hg and Mean BP values to 133±14 (p=0.07), 79±9 (p=0.06), respectively.

Office-measured BP values (sys or dia) were reduced >10 mm Hg in 121/146 pts (84.3%) and were found normal in 82/146 pts (56%). Peak BP values were reduced >10 mm Hg in 101/146 pts (69%) and were within normal limits in only 40/146 pts (27%).

Mean BP values were returned to normal in 110/146 (75%) pts.

Conclusions: These data indicate that when evaluated by ABPM antihyperten-
sive treatment results less efficacious then when traditionally evaluated.

AMBULATORY BLOOD PRESSURE MONITORING

Masked hypertension and atherogenesis: the impact on apelin and relaxin plasma levels

D. Papadopoulo1, O. Papazachou2, I. Mourozis1, A. Kotrotsou1, M. Daskalaki1, C. Thomopoulos1, E. Sanidas1, D. Perrea1, I. Mourouzis1, A. Kotrotsou1, E.B. Kaya1, K. Aytemir1, A.U. Demir1, L. Tokgozoglu1, A. Oto1, M. Daskalaki2, C. Thomopoulos2, E. Sanidas2, D. Perrea2, I. Mourouzis2, A. Kotrotsou2, E.B. Kaya2, K. Aytemir2, A.U. Demir2, L. Tokgozoglu2, A. Oto2, 1Hacettepe University, Faculty of Medicine, Ankara, Turkey; 2Hacettepe University, Faculty of Medicine, Department of Cardiology, Ankara, Turkey

Purpose: Recent evidence demonstrates that masked hypertension (MH) is a significant predictor of cardiovascular disease, while hypoaipelinemia and hypore-
laxinemia may contribute to vascular damage accelerating atherogenesis.

Methods: Aims of our study was to examine the apelin and relaxin plasma levels in patients with renal transplants (Rtx). In pediatric Rtx, high prevalence of masked and nocturnal hypertensive treatment.

The prevalance of masked hypertension and blood pressure values in patients with renal transplantation

M. Kayrak1, E.E. Gul1, C. Kaya2, K. Turkenm1, Y. Solak1, R. Yazici3, I. Gul1, L. Albintep1, S. Turk1, K. Ozdemir1, 1 Selcuk University Meram, Faculty of Medicine, Konya, Turkey; 2 Meram Faculty of Medicine, Konya, Turkey; 3 Meram Research and Training Hospital, Konya, Konya, Turkey

Purpose: Arterial hypertension is a risk factor affecting graft function in renal transplants (Rtx). In pediatric Rtx, high prevalence of masked and nocturnal hyp-
ertension was reported. Most of the Rtx had a history of hypertension and some of them are normotensive in outpatient control, however home blood pressure
levels are higher. Masked hypertension (MHT) is defined as a normal office blood pressure but an elevated ambulatory blood pressure. Use of ambulatory-

blood pressure monitoring (ABPM) enables the identification of MHT. Previous

reports have demonstrated the role of MHT in the outcome of hypertensive pa-
ients. However, the true prevalance of MHT in Rtx is still unknown.

Methods: The study enrolled Rtx with normal office blood pressure level (SPB<140/90mmHg) admitted to the outpatient clinic of Nephrology and Transplantation over a year. ABPM was performed in all patients during 24-h pe-
riod. MHT was defined as normal office BP associated with daytime ambulatory hypertension(SBP<140/80mmHg).

Results: The prevalence of MHT and nocturnal hypertension in our group were 49% and 61%, respectively. Fifty-four (54%) patients had a history of HT. Fifty-

eight (58%) patients were being treated with antihypertensives medications. Non-
dipping was present in 81.5% of patients. There were no significant difference regarding demographic and clinical features between patients with and without MHT (Table).

Table 1

<table>
<thead>
<tr>
<th>Age, years</th>
<th>With MHT (n=50)</th>
<th>Without MHT (n=50)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>40±11</td>
<td>42±11</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>123±12</td>
<td>122±11</td>
<td>0.79</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>79±6</td>
<td>77±7</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26±5</td>
<td>26±5</td>
<td>0.71</td>
</tr>
<tr>
<td>Systolic diastolic blood pressure</td>
<td>146/80</td>
<td>150/75</td>
<td>0.13</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>30</td>
<td>24</td>
<td>0.16</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>8</td>
<td>4</td>
<td>0.16</td>
</tr>
<tr>
<td>CCB, n</td>
<td>30</td>
<td>28</td>
<td>0.41</td>
</tr>
<tr>
<td>CB, n</td>
<td>13</td>
<td>10</td>
<td>0.32</td>
</tr>
</tbody>
</table>

BMI, body mass index; CCB, calcium channel blocker; BB, beta blocker.

Conclusion: We demonstrated an increased prevalence of MHT and BP vari-
bility in Rtx population. These results may explain high cardiovascular events in Rtx patients. Therefore routine recommendation of ABPM in Rtx patients may be reasonable.

Impact of nocturnal continuous positive airway pressure therapy on ambulatory blood pressure in patients with obstructive sleep apnea and prehypertension

H. Yorgun1, G. Kabako2, E. Kirmizioglu2, U. Canpolat3, A.H. Ates3, E.B. Kaya1, K. Aytemir1, A.U. Demir1, L. Tokgozoglu1, A. Oto3, 1Selcuk University, Faculty of Medicine, Ankara, Turkey; 2Hacettepe University, Faculty of Medicine, Department of Cardiology, Ankara, Turkey

Background: We aimed to investigate the short term effects of CPAP treatment on blood pressure (BP) and nondipper or dipper status in OSAS patients without a prior diagnosis of hypertension (HT).

Methods: We included a total of 24 patients (19 male, mean age: 48±7.10 years). The study group was divided into 2 groups; group 1 with mild-moderate OSAS (AHI<30) and group 2 with severe OSAS (AHI>30). Patients with OSAS were assigned to treatment with CPAP. An overnight polysomnography was performed by a computerized system. A 24-h ambulatory monitor (was used to record BPs in all patients.

Results: Mean ambulatory 24 hour systolic and diastolic BPs were 126±6.9 mm Hg and 79±5±10 mm Hg respectively. CPAP treatment significantly decre-
ased 24 hour mean BP after 12 weeks irrespective of AHI (89±±7.6 mm Hg baseline vs. 82.9±7.3 mm Hg after 12 weeks, p≤0.0001). After 6 weeks CPAP treat-
ment, non-dippers reduced to 16.6% and at the end of 12 week CPAP treat-
ment, 12.5% of the patients were non-dipper (p=0.008). Multiple linear regression analysis revealed that male gender, Epworth sleepiness scale, apnea-hypopnea index, smoking and mean 24 hour BP were the predictors of BP reduction in pa-

ents between baseline and after 12 week CPAP (p<0.05)

Multiple linear regression analysis for the predictors of BP reduction after CPAP therapy

<table>
<thead>
<tr>
<th>β-coefficient</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male</td>
<td>-5.76</td>
</tr>
<tr>
<td>Blood ESS score</td>
<td>-0.35</td>
</tr>
<tr>
<td>AHI</td>
<td>-0.14</td>
</tr>
<tr>
<td>Baseline BMI (kg/m²)</td>
<td>-0.29</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2.66</td>
</tr>
<tr>
<td>Alcohol consumpton</td>
<td>5.59</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-4.7</td>
</tr>
<tr>
<td>Baseline 24 MBP (mmHg)</td>
<td>-0.70</td>
</tr>
</tbody>
</table>

Conclusion: Effective CPAP therapy reduces BP levels in OSAS patients with-
out hypertension and improves dipper-nondipper status.
Metabolic syndrome increases morning blood pressure surge

E. Chatzistamatiou1, G. Moustakas1, E. Androulakis1, D. Tousoulis2, A. Avgeropoulou1, N. Kaloudis1, M. Divani1, D. Liakos3, C. Stelanadis1, I. Kallikazaros1,2. Hippokration General Hospital, Cardiology Department, Athens, Greece; 2Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece

Purpose: Large scale studies suggest that systolic blood pressure morning surge is an independent predictor of target organ damage. Aim of our study was to investigate associations between 24hr ambulatory blood pressure (ABPM) levels and morning surge in never-treated essential hypertensive (EH) patients with and without metabolic syndrome (MS).

Methods: We studied 366 consecutively newly diagnosed EH patients stage I-III (age 51±12 years, 60% males) without prevalent cardiovascular disease. In all participants anthropometric data were recorded. Also, all subjects underwent a 24-hour ambulatory blood pressure monitoring (ABPM) and morning surge index was calculated as: the mean systolic blood pressure (SBP) during the 2 hours after awakening minus mean SBP during the 1 hour that included the lowest sleep BP. Heart rate variability was calculated as the ratio of day-night mean heart rate difference normalized to mean day heart rate. According to ATP III criteria, the study cohort was divided in two groups: Group A (n=210, MS-) and Group B (n=156, MS+).

Results: The two groups did not differ regarding age, sex, smoking and snoring status, alcohol and coffee consumption, serum cholesterol, office systolic and diastolic blood pressure and 24-h ABPM blood pressure levels. Group B compared to A exhibited increased BMI (31.3±4 vs. 26.3±3, p<.001), 24hr average (74.9±9 vs. 72.8±8, p=0.19) and night (66±6 vs. 63.8±p=0.02) heart rate, heart rate variability (12.3±7 vs. 15.6±7, p=0.037) and morning surge index (23.3±13 vs. 19.1±12, p=0.009).

Conclusion: In never-treated EH patients, the presence of metabolic syndrome unfavourably affects autonomic function as expressed not only by decreased HR variability, but also by increased blood pressure morning surge. These autonomic disturbances may be the link between MS, subclinical target organ damages and prevalent CVD.

Establishment of reference values for central blood pressure estimated by Omron HEM-9000AI

S. Tanaka1, H. Takase2, T. Sugiyama1, S. Yamashita1, Y. Doi1, G. Kimura1,1, Nagoya City University, Graduate School of Medical Sciences, Dept of Cardio-Renal Medicine & Hypert., Nagoya, Japan; 2Enshu Hospital, Hamamatsu, Japan

Purpose: Although central blood pressure (BP) is more closely associated with cardiovascular events than conventional brachial BP, a wider implementation of central BP into clinical practice is hampered by the lack of established reference values. Recently, an automated device for the estimation of central BP has been introduced (Omron HEM-9000AI). This noninvasive estimation shows close correlation with that by Sphygmocor device, but the Omron device requires its own reference values because of technological differences between Sphygmocor and Omron. Thus, the present study was designed to establish normal and reference values for central BP estimated by the Omron device.

Methods: Consecutive 10756 subjects (55.3±12.5 years) who visited our hospital for a health checkup were enrolled in this study. Of these, 7348 subjects received no anti-hypertensive, anti-diabetic, or lipid-lowering drug treatment, constituting the reference value population. Subjects with no cardiovascular risk factors and that were in the optimal or normal brachial BP categories (n=2672) were selected to establish normal values.

Results: Estimated central BP was higher than brachial BP and was significantly correlated with age and brachial BP. Reference and normal values of central BP were established according to age decade (table) and brachial BP categories. Reference values (mmHg, mean±2SD) were 133.5±18.6 in optimal, 128.6±14.6 in normal, 138.4±16.8 in high normal, and 155.3±27.9 in hypertension categories and normal values were 112.6±19.2 in optimal and 129±14.9 in normal BP categories.

Enhanced external counterpulsation has no lasting effect on blood pressure

O. May, W.A.M. Khair. Region Hospital Herning, Herning, Denmark

Background: Enhanced external counterpulsation (EECP) has been reported to reduce blood pressure (BP) using clinic BP readings. Patients referred for EECP due to refractory angina pectoris were consecutively included in the study and treated with EECP for 1 hour 5 days a week in 7 weeks. The ABP were measured for 24 hours using a Spacecap Ultrafine 90217 device 2 months before an EECP course, just before the EECP course, just after, 3 and 12 months after EECP. The anti-hypertensive medication was held constant during the study period. Changes in BP were tested by repeated measure analysis and changes in anti-hypertensive medication by Friedmans test for related samples.

Conclusions: The present study is the first to establish reference and normal values of central BP estimated by the Omron HEM-9000AI. This makes an important step in the implementation of central BP as a clinical tool in the diagnosis and management of hypertension.

Enhanced external counterpulsation (EECP) has no lasting effect on blood pressure

Enhanced external counterpulsation has no lasting effect on blood pressure

Downloaded from https://academic.oup.com/eurheartj/article-abstract/33/suppl_1/655/430798 by guest on 18 April 2019
Results: Fifty patients were included, 72% were males, mean age was 63 years, mean BMI was 29.7 kg/m² and 64% had hypertension. The mean baseline clinic BP was 118/75 mm Hg. Fifty two percent were treated with ACE/ARB, 90% betablocker, 68% calcium antagonist, 92% long acting NTG and 42% with diuretics. The CCS class improved from mean 2.6 to 1.5. No significant change was found in medication. The mean daytime and night time ABP did not change significantly during the study period (p>0.05), see table. Further, when controlling for quartiles of baseline ABP level no interaction was found between ABP and baseline level.

Conclusion: EEEP treatment has no lasting effect on blood pressure.

Effect of atmospheric pressure on blood pressure

U.I. Cieslik-Guerra1, M. Kaminiski2, J. Chlapinski2, W. Maranda2, M. Pietrowicz2, E. Trozo2, B. Uznanska-Loch1, T. Rechinski2, M. Kurpca1, A. Napieralski2, 1Chair of Cardiology, Medical University of Lodz, Biegalski Hospital, Lodz, Poland, 2Technical University of Lodz, Department of Microelectronics and Computer Science, Lodz, Poland

Purpose: Weather conditions are well known as a factors which can influence health of human. Sensitivity to changes in atmospheric pressure (AP) can be dangerous, especially for patients (pts) with labile hypertension (HA) and cause difficulties in choosing appropriate pharmacotherapy. Previous studies showed correlation between AP and home BP. In our study we tried to determine relationship of AP and blood pressure (BP) in 24-hour ambulatory monitoring (ABPM).

Methods: The authors conducted a statistical analysis of data recorded with ABPM in pts with HA living near the site, and the weather data recorded by a local weather station from Jan 2009 to Aug 2010. The readings from the weather station were performed with a frequency of 1 measurement per minute.

The group of pts consisted of 416 people (mean age - 60.5 years, women – 191). Systolic and diastolic BP were measured at intervals of 15 min (30 min at night). For the study were included only pts with at least 50 parallel measurements of BP and AP.

In the first stage of statistical analysis authors determined the Pearson correlation (r) between systolic BP and AP. In order to explain the observed correlations was examined the impact of the season of a year, distribution of age groups and distribution of dippers and non-dippers groups.

Result: In large proportion of pts 24% (110 pts), systolic BP shows a strong dependence on AP (r > 0.4). 34.8% of pts (145 pts) systolic BP shows a weak correlation with AP (0.2 < r < 0.4). In group of 193 pts BP remain without correlation to AP.

In analysis of subgroups it was noticed that strong correlations with AP occurred only in groups of dippers and extreme dippers (Table I).

Table I

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of investigation (all/women)</th>
<th>Age</th>
<th>r (p-value)</th>
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<tbody>
<tr>
<td>Reverse Dipper</td>
<td>70/28</td>
<td>69.4±10.34</td>
<td>0.24±0.19 (0.27±0.30)</td>
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<td>Non-Dipper</td>
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<td>16</td>
<td>58.1±13.34</td>
<td>0.44±0.21 (0.01±0.26)</td>
</tr>
<tr>
<td>All</td>
<td>448/201</td>
<td>60.4±16.43</td>
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</table>

1. correlation coefficient; p-value: 0.25 – statistical significance.

Conclusion: Systolic BP in ABPM is related to AP in 58.8% of study population. The strongest correlation was observed in pts with excessive nocturnal decline in BP (3.8%). Pts with labile HA and evidence of sensitivity to changes in AP should monitor forecasts and adequately adapt pharmacotherapy.

Reproducibility of ambulatory blood pressure monitoring in patients with coronary heart disease

S. Rossa, I. Sudano, F. Ernefelt, P. Kaiser, A. Hirt, T.F. Lüscher, F. Ruschitzka, G. Noll. University Hospital Zurich, Cardiovascular Center, Department of Cardiology, Zurich, Switzerland

Purpose: The ambulatory blood pressure monitoring (ABPM) is a useful tool for the diagnosis and control of blood pressure as well as for monitoring the response to antihypertensive therapy. We aimed to assess the reproducibility of the circadian blood pressure (BP) pattern (24 h, daytime and nighttime BP and heart rate -HR), the categorization as dipper and non-dipper and the morning BP peak in three ABPM obtained in patients with coronary heart disease (CHD).

Methods: We performed a retrospective analysis of the reproducibility of three repeated ABPM obtained in 49 patients with coronary heart disease (age: 61±7.9 years, 41 males, 36 hypertensive) enrolled in two previous studies using Tracker NIBP2 devices (Delmar,Del Mar Reynolds Medical, Hertford, UK). The patients underwent ABPM on three separate days, on a typical weekday with normal daily activity. The nighttime was determined according to the information obtained by patient. All patients had a history of CHD and a stable cardiovascular medication during the period of the three measurements.

Results: The evaluation of the reproducibility of the variables measured in three recordings was performed by analysis of variance for repeated measurements (ANOVA, Pillai’s trace test) and by Pearson’s correlation coefficient. Values are expressed as mean±standard deviation. We found no significant variance in 24-hour day and night BP and HR as well as morning BP peak (Table I). The categorization as Dipper and Non-Dipper was also highly reproducible (p = 0.852; ns).

Conclusion: In conclusion our data confirm that the reproducibility of the circadian blood pressure pattern in 24 h recordings in patients with CHD is significantly reliable.

Conclusion: EECP treatment has no lasting effect on blood pressure.

Effect of atmospheric pressure on blood pressure

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Purpose: The ambulatory blood pressure monitoring (ABPM) is a useful tool for the diagnosis and control of blood pressure as well as for monitoring the response to antihypertensive therapy. We aimed to assess the reproducibility of the circadian blood pressure (BP) pattern (24 h, daytime and nighttime BP and heart rate -HR), the categorization as dipper and non-dipper and the morning BP peak in three ABPM obtained in patients with coronary heart disease (CHD).

Methods: We performed a retrospective analysis of the reproducibility of three repeated ABPM obtained in 49 patients with coronary heart disease (age: 61±7.9 years, 41 males, 36 hypertensive) enrolled in two previous studies using Tracker NIBP2 devices (Delmar,Del Mar Reynolds Medical, Hertford, UK). The patients underwent ABPM on three separate days, on a typical weekday with normal daily activity. The nighttime was determined according to the information obtained by patient. All patients had a history of CHD and a stable cardiovascular medication during the period of the three measurements.

Results: The evaluation of the reproducibility of the variables measured in three recordings was performed by analysis of variance for repeated measurements (ANOVA, Pillai’s trace test) and by Pearson’s correlation coefficient. Values are expressed as mean±standard deviation. We found no significant variance in 24-hour day and night BP and HR as well as morning BP peak (Table I). The categorization as Dipper and Non-Dipper was also highly reproducible (p = 0.852; ns).

Conclusion: In conclusion our data confirm that the reproducibility of the circadian blood pressure pattern in 24 h recordings in patients with CHD is significantly reliable.
Real-world primary PCI with bivalirudin: a report from the prospective, multi-centric EUROVISION registry

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Purpose: In primary PCI, bivalirudin (BIVA) is superior to heparin+GPIs in reducing bleeding and improving survival. However, a higher incidence of acute stent thrombosis was observed in BIVA-treated patients. The purpose of this analysis was to evaluate 30-day outcomes from a real-world STEMI population from the EUROVISION (EUR) registry treated with a BIVA alone strategy.

Methods: Among the 2018 EUR BIVA-treated patients, 663 underwent primary PCI for STEMI. Outcomes measures were 30-day death, re-infarction (MI), stroke, stent thrombosis, urgent revascularization (URV), bleedings, and thrombocytopenia. The net adverse cardiovascular events (NACE) rate combining death, MI, URV and major bleeding was also calculated.

Results: Thirty-day mortality from EUR patients BIVA infusion was frequently continued post-PCI (62%, median 122 min, 60-296 IQR). Pre-PCI thienopyridine loading was performed in 95%, GPI used in 5%, and radial approach performed in 30% of cases. STEMI patients in EUR were older (p<0.001), but with similar 30-day mortality to HORIZONS-AMI treated patients. Thirty-day outcomes (MI, URV or bleedings) were lower in EUR resulting in lower NACE rates compared with HORIZONS-AMI (Table 1). In EUR patients there were no acute (<24 hrs) stent thrombosis cases and no cases of thrombocytopenia.

Conclusions: Real world data from EUR confirm the HORIZONS-AMI trial (HOR) due to significant reduction in bleedings and improved survival. However, a higher incidence of acute stent thrombosis was observed in BIVA-treated patients. The purpose of this analysis was to evaluate 30-day outcomes from a real-world STEMI population from the EUROVISION (EUR) registry treated with a BIVA alone strategy.

P5045

Thrombus aspiration reduces plaque volume in non-ST elevation acute coronary syndromes: the reduction of myocardial necrosis achieved with nose-dive manual thrombus aspiration study

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Purpose: Thrombus and plaque microembolization is the main cause of myocardial damage during percutaneous coronary intervention with stenting (S-PCI). Thrombus aspiration (TA) has proven useful in limiting myocardial damage in S-PCI elevation myocardial infarction (STEMI), but its role in non-ST elevation acute coronary syndromes (NSTE-ACS) is not yet defined. We hypothesized that TA reduces the atherothrombotic burden in such patients before S-PCI, thus having the potential of limiting periprocedural myocardial damage.

Methods: Patients with >1 “high-grade” (>90%) lesions at coronary angiography subjected to PCI for a NSTE-ACS were submitted to TA before S-PCI. Exclusion criteria were the presence of visible thrombus, total occlusion, degenerated vein graft, restenotic lesions. TA successfully crossed the lesion in 38/45 patients. We evaluated the effect of TA on thrombus burden and lesion characteristics by angiography and intravascular ultrasound (IVUS) before and after TA and after S-PCI. The aspirated material was also processed for histology.

Results: Mean patients’ age was 65±10 years; 82% were male; 34% underwent PCI for a recent STEMI; 64% for a NSTE-ACS. Mean lesion and stent lengths were 25±1.1 and 28±1.9 mm, respectively. Drug-eluting stents were used in 74% of cases. Peak CK-MB and troponins-I were 23±3.9 mg/mL and 9.2±23.13 ng/mL, respectively. Main findings related to the effects of TA are summarized in the Table. The aspirated material was composed of fibrin in 45% of cases, red thrombus in 19%, plaque fragments in 25%, with a lymphocyte infiltration in 16%, and signs of intraplaque hemorrhage in 16%.

Effects of TA on angiographic and IVUS

Conclusion: TA reduces the “mobilizable” atherothrombotic plaque burden and may be safely performed before S-PCI in high-risk NSTE-ACS pts as an alternative to balloon predilatation. These data are encouraging for a beneficial role of TA in reducing peri-procedural myocardial damage also in S-PCI in the setting of NSTE-ACS.
infarction (MI) size. The objective of our study was to determine whether PC has a long-term benefit on left ventricular (LV) remodelling and function in optimally treated patients with MI.

Methods: Patients presenting, within 12 h of the onset of chest pain, with a first STEMI, and for whom the clinical decision was made to perform revascularization by percutaneous coronary intervention, were eligible for enrolment. After reperfusion by direct stenting, 47 patients were randomly assigned to either a control (no intervention; n=23) or a post-conditioned group (repeated inflation and deflation of the angioplasty balloon; n=24). MI size was assessed by cardiac enzyme release during 72 h after reperfusion. At 3 days and 6 months after MI, LV size and function was evaluated by echocardiography.

Results: The 2 groups had similar ischemic duration, area at risk and medical treatment during and after reperfusion. PC significantly reduced MI size (~34% compared to controls). At Day7 after MI, no difference was observed on LV size and function (LV ejection fraction (EF): 55.8% vs Controls, 54.1±10% in PC, p=0.7). At 6 months, controls displayed LV end-diastolic volume enlargement compared to initial echocardiography (91.±29 vs. 100.3±30 ml, respectively; p=0.02) and no significant improvement on LVEF or wall motion score index (Figure 1). In contrast, PC patients displayed no LV enlargement (90.±28 vs. 95.3±35 ml, respectively; p=0.27) and improved both their LVEF and wall motion score index compared to the initial echocardiography (Figure 1, p=0.05 vs baseline).

Conclusions: Ischemic PC on top of optimal therapy reduces MI size in patients with acute MI and improves remodelling at 6 months compared to controls.

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Enoxaparin is superior to unfractionated heparin in primary PCI for STEMI: results of the prespecified per-protocol analysis of the ATOLL trial

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Background: The ATOLL trial evaluated the efficacy and safety of intravenous enoxaparin versus unfractionated heparin (UFH) in the contemporary interventional management of STEMI. Patients who had received any anticoagulation before randomisation could not be enrolled. Cross over to a different anticoagulant after randomization was not allowed. Enoxaparin was shown to be significantly better than UFH for all ischemic endpoints without safety issue but the 17% risk reduction of the primary endpoint of death, composite of MI, procedure failure or major bleeding was not significant (p=0.06)

Objectives and methods: To present the results of the pre-specified per-protocol analysis excluding patients that received more than one heparin (protocol violation). A total of 805 patients (87.8%) were treated according to the protocol with consistent anticoagulation using enoxaparin (n=403) or UFH (n=397). The per-protocol analysis as for the intent-to-treat analysis were performed in this cohort of patients.

Results: Enoxaparin resulted in significantly reduced rates of the primary end-point and main secondary endpoint (table). The net clinical benefit of death was also reduced with enoxaparin (table). There were favorable trends for enoxaparin on bleeding complications and blood transfusion as well.

Conclusions: The per-protocol analysis of the ATOLL trial confirms and reinforces the main findings of the study. Intravenous enoxaparin was superior to UFH on both the primary and secondary endpoints. Most of the benefit is observed on ischemic endpoints. However, in a study with predominant radial access, bleedings tended also to be less frequent on enoxaparin than on UFH. The net clinical benefit was significantly improved with enoxaparin.

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Mechanical postconditioning during primary percutaneous coronary intervention (PPCI) may cause thrombus dislodgement with distal embolization and its combination with thrombus aspiration on microvascular obstruction (MVO) and infarct size (IS) have not been assessed. We assessed the short-term effects of mechanical ischemic postconditioning with or without thrombus aspiration on early and late MVO size, IS and left ventricular ejection fraction (LVEF) in acute STElevation myocardial infarction (STEMI) patients.

Aims: Mechanical postconditioning during primary percutaneous coronary intervention (PPCI) may cause thrombus dislodgement with distal embolization and its combination with thrombus aspiration on microvascular obstruction (MVO) and infarct size (IS) have not been assessed. We assessed the short-term effects of mechanical ischemic postconditioning with or without thrombus aspiration on early and late MVO size, IS and left ventricular ejection fraction (LVEF) in acute STElevation myocardial infarction (STEMI) patients.

Methods and results: Fifty-one patients undergoing PPCI for a first STEMI with TIMI grade flow ≥ 1 and no collaterals were randomized to ischemic postconditioning (n=26) or controls (n=25). Ischemic postconditioning consisted in the application of four consecutive cycles of 1 minute balloon occlusion, each followed by 1 minute deflation at the onset of reperfusion. Thrombus aspiration was applied at the discretion of the treating physician. MVO size, IS, LVEF and volumes were assessed by contrast enhanced cardiac-MRI 72 hours after reperfusion.

Postconditioning was associated with smaller early (3 minutes post-contrast) and late (10 minutes post-contrast) MVO size (5.1±6.7 vs. 11.3±11.0 g in controls for early MVO; P=0.02; and 2.5±4.6 vs 5.9±6.1 g in controls for late MVO; P=0.03) even after adjustment for thrombus aspiration. Overall, there was a non-significant
Addition of ivabradine during beta-blockers titration improves systolic and diastolic LV function in patients with recent Q-wave myocardial infarction

Y.A. Lutay, A.N. Parkhomenko, O.I. Irkin, A.A. Stepura. National Scientific Center "M.D. Strazhesko Institute of Cardiology, MAS of Ukraine", Kiev, Ukraine

Heart rate (HR) is a powerful predictor of mortality and heart failure (HF) in pts with acute myocardial infarction (AMI). β-blockers are the first line treatment for these pts but time is needed for their titration and side effects can limit their use in appropriate dose. Ivabradine may be a good alternative for HR reduction during β-blockers titration. 80 pts with recent (36-72 h after symptoms onset) Q-wave AMI and HR > 80 bpm were studied. β-blockers were initiated in all the pts. 40 pts were randomized for ivabradine 5mg bid in addition to standard treatment and 40 pts were controls. Dosage of ivabradine was increased to 7.5 mg if HR remained > 70 bpm after 24 hrs of treatment. EF (86.3%) pts had anterior AMI and 56.5% pts had symptoms of acute heart failure (Killip II). Study and control groups did not differ in regards of baseline, clinical characteristics, reperfusion and initial treatment. Standard two-dimensional, M-mode, spectral, color and tissue Doppler were performed at baseline and day 7. Ivabradine significantly decreased HR after the first 24 hrs of treatment and helped to keep HR 7-10 bpm lower than in control group throughout the period of investigation. The effects of chronic ipt (without any changes of EDI) and improved LV diastolic function. At day 7, early diastolic velocity of lateral LV corner (E') was significantly higher in ivabradine group than in controls. Ivabradine also prevented left atrium dilatation.

Conclusions: In the present study cohort, poor pre TIMI grade seemed to result to the late exacerbated microcirculation. In patients with STEMI showing poor pre-pCI TIMI grade, thrombectomy and distal protection may be promising remedies for the myocardial salvage with lower risk of bleeding complication.

Table 1

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Total</th>
<th>Patients with thrombectomy and/or distal protection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TIMI 0-1</td>
<td>TIMI 2-3</td>
</tr>
<tr>
<td>LVEF baseline (%)</td>
<td>48.4±11.4</td>
<td>48.6±12.4</td>
</tr>
<tr>
<td>LVEF follow up (%)</td>
<td>54.9±11.7</td>
<td>52.6±11.2</td>
</tr>
<tr>
<td>LVEF delta (%)</td>
<td>6.5±12.6</td>
<td>7.7±10.4</td>
</tr>
<tr>
<td>TIMI Grade</td>
<td>3 at post PCI (%)</td>
<td>66.0</td>
</tr>
<tr>
<td>TIMI Grade</td>
<td>3 at follow up (%)</td>
<td>88.2</td>
</tr>
<tr>
<td>MBG Grade</td>
<td>3 at post PCI (%)</td>
<td>31.3</td>
</tr>
<tr>
<td>MBG Grade</td>
<td>3 at follow up (%)</td>
<td>45.3</td>
</tr>
</tbody>
</table>

Conclusions: The effects of chronic IPT on global and regional LV function and infarct composition in a preclinical porcine model of reperfused infarction.

Methods: Fourteen pigs underwent proximal LCx ligation for 2h followed by reperfusion to induce a transmural infarction, and were instrumented with a pacemaker connected to an epicardial LV lead positioned in the anterior peri-infarct zone. Three days later, LV function and infarct-size were assessed with 3.0-Tesla cardiac MRI and animals were stratified into Control therapy and IPT groups (after which all pigs survived). IPT consisted of LV pacing twice daily for 3 x 5 min separated by 5 min of normal sinus rhythm until 5 wk post-implantation, after which follow-up cardiac MRI was obtained and myofibroblasts were quantified in the infarct zone, using an unbiased muscle actin staining.

Results: Although IPT had no significant effect on global LV remodeling or function (data not shown), or infarct mass, it markedly influenced infarct geometry (Table). Thus, in control pigs the reduction in infarct mass over time was principally due to infarct thinning. In contrast, in the IPT pigs it was principally due to decreases in circumference and longitudinal length (both p<0.05) with no significant change in infarct thickness. Subsequently, histological scoring of myofibroblasts in the infarct zone revealed an increase in myofibroblasts in IPT animals (10.9±2.1%) compared to controls (5.4±1.6%, p<0.05).

Conclusions: IPT favorably modified infarct remodeling, likely by enhancing myofibroblast numbers in the infarct zone.

The utility of thrombectomy and distal protection in patients with ST-segment elevation myocardial infarction showing poor coronary artery flow prior to primary percutaneous coronary artery intervention

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Introduction: Previous studies had shown that poor coronary artery flow prior to primary percutaneous coronary artery intervention (PCI) for ST-elevation myocardial infarction (STEMI) is associated with exacerbated clinical outcomes, although the positive clinical results of the facilitated percutaneous coronary intervention have not been shown. The aim of this study was to evaluate the efficacy of thrombectomy and/or distal protection device in PCI for STEMI patients showing poor pre TIMI grade.

Methods: Out of 696 STEMI patients enrolled either in the two multicenter randomized trials (VAMPIRE trial: tested the efficacy of thrombectomy or thrombectomy or ASPARA-GUS trial: tested the efficacy of distal protection device), 185 lesions in 185 patients who underwent the primary PCI for proximal or mid left anterior descending coronary artery lesion and have complete sets of angiographic data (Ejection fraction [EF] evaluated by left ventriculography, myocardial blush grade [MBG] and TIMI grade) at baseline and 6-months follow-up were evaluated. Delta EF was calculated by (follow up - baseline).

Results: Table shows the results. MBG3 was achieved more frequently at pre TIMI 2-3 group. However, in patients who underwent aspiration and/or distal protection, the difference in MBG-3 rate was insignificant between pre TIMI 0-1 and 2-3 group.

Conclusions: In patients with recent Q-wave AMI and HR > 80 bpm were studied. β-blockers were initiated in all the pts. 40 pts were randomized for ivabradine 5mg bid in addition to standard treatment and 40 pts were controls. Dosage of ivabradine was increased to 7.5 mg if HR remained > 70 bpm after 24 hrs of treatment. EF (86.3%) pts had anterior AMI and 56.5% pts had symptoms of acute heart failure (Killip II). Study and control groups did not differ in regards of baseline, clinical characteristics, reperfusion and initial treatment. Standard two-dimensional, M-mode, spectral, color and tissue Doppler were performed at baseline and day 7. Ivabradine significantly decreased HR after the first 24 hrs of treatment and helped to keep HR 7-10 bpm lower than in control group throughout the period of investigation. The effects of chronic ipt (without any changes of EDI) and improved LV diastolic function. At day 7, early diastolic velocity of lateral LV corner (E') was significantly higher in ivabradine group than in controls. Ivabradine also prevented left atrium dilatation.

Table 1

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline (N=128)</th>
<th>Control (N=57)</th>
<th>p</th>
<th>TIMI 0-1 (N=66)</th>
<th>TIMI 2-3 (N=27)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDI, mm²</td>
<td>58.8±1.6</td>
<td>59.3±1.4</td>
<td>ns</td>
<td>59.1±1.5</td>
<td>59.7±1.8</td>
<td>ns</td>
</tr>
<tr>
<td>EF %</td>
<td>39.3±0.8</td>
<td>44.4±0.7</td>
<td>p=0.008</td>
<td>40.7±1.1</td>
<td>42.2±1.0</td>
<td>ns</td>
</tr>
<tr>
<td>LA, mm</td>
<td>36.2±0.5</td>
<td>37.5±0.6</td>
<td>ns</td>
<td>35.9±0.6</td>
<td>38.7±0.7</td>
<td>p=0.045</td>
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<tr>
<td>T1, ms</td>
<td>109.6±0.1</td>
<td>98.0±0.1</td>
<td>ns</td>
<td>106.6±1.0</td>
<td>103.0±1.1</td>
<td>ns</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>153.7±9.7</td>
<td>165.3±7.9</td>
<td>ns</td>
<td>148.9±5.3</td>
<td>152.3±8.0</td>
<td>ns</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>89.7±3.9</td>
<td>94.3±5.4</td>
<td>ns</td>
<td>86.3±5.8</td>
<td>89.8±3.9</td>
<td>ns</td>
</tr>
<tr>
<td>E', cm/s</td>
<td>6.8±0.4</td>
<td>8.1±0.5</td>
<td>p=0.036</td>
<td>6.6±0.5</td>
<td>6.3±0.4</td>
<td>ns</td>
</tr>
<tr>
<td>E'/E</td>
<td>0.9±0.6</td>
<td>9.0±0.4</td>
<td>p&lt;0.002</td>
<td>11.0±0.7</td>
<td>9.3±0.5</td>
<td>ns</td>
</tr>
</tbody>
</table>

In patients with recent Q wave AMI and HR >80 bpm ivabradine can be used during β-blockers up titration for LV systolic and diastolic function improvement.

Table 1

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Infarct mass (g)</th>
<th>Infarct thickness (mm)</th>
<th>Infarct length (mm)</th>
<th>Infarct circumference (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>IPT</td>
<td>Control</td>
<td>IPT</td>
</tr>
<tr>
<td>Post MI</td>
<td>Baseline (N=128)</td>
<td>17.6±1.4</td>
<td>17.1±1.2</td>
<td>6.2±0.2</td>
</tr>
<tr>
<td>Post MI</td>
<td>Control</td>
<td>IPT</td>
<td>Control</td>
<td>IPT</td>
</tr>
<tr>
<td>1 week (1 from BL of FU 5 weeks)</td>
<td>6.5±0.9</td>
<td>7.4±1.1</td>
<td>10.0±0.6</td>
<td>9.3±0.6</td>
</tr>
</tbody>
</table>

Data are mean ± SD; Control, n=57; IPT, n=6; *p<0.05, change from corresponding Baseline; †p<0.05, change in IPT versus change in Control.
Gender differences in major bleeding with bivalirudin versus heparin during primary PCI in Acute Myocardial Infarction: results from the HORIZONS-AMI trial

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Purpose: Previous studies have shown that women are at increased bleeding risk post AMI and primary PCI. Bivalirudin (BIV) has been shown to reduce bleeding complications compared with heparin plus glycoprotein IIb/IIIa inhibitor (HEP + GPI). The purpose of this study was to examine the differential impact of BIV on short- and long-term outcomes (>1 year) in women vs. men.

Methods: We examined 3-year outcomes from the HORIZONS-AMI trial according to sex and assignment to BIV vs. HEP + GPI. We used Cox proportional-hazards methods with stepwise selection using entry and exit criteria of p < 0.1, to determine the independent predictors of major bleeding among women. Candidate variables tested were assignment to BIV vs. HEP + GPI, age, sex, body weight, diabetes, prior history of hypertension, history of smoking, prior MI, prior PCI, prior CABG, Killip class >1, baseline anaemia, creatinine, radial vs. femoral access, and symptom onset to ballooning time.

Results: Women (n=842), as compared with men (n=2760), were significantly older and had higher prevalence of hypertension and hyperlipidaemia but were less likely to have a prior history of MI, PCI, CABG or smoking (all p < 0.05). BIV was associated with reduced in-hospital and 30-day major bleeding in both men and women (all p < 0.05). At 3 years, men receiving BIV compared with HEP + GPI had reduced major bleeding (5.3% vs. 9.1%, p=0.0002), however the difference was not significant in women (12.3% vs. 15.1%, p=0.16).

Conclusion: BIV showed a trend towards reduced major bleeding in women (Figure 1).<6 hours. In the former group rapid rule-out was based on a single measurement using hs-cTnT, and in the latter group on two hs-cTnT values, at presentation and at 3 hours.

Results: Of all late presenters (n=619), 19% (n=117) received the final diagnosis of NSTEMI, compared to 17% (n=214) of early presenters (n=1252). Six late presenters and two early presenters with the final diagnosis of NSTEMI had hs-cTnT levels below the cutoff of 0.014 μg/L. The overall negative predictive value (NPV) applying only the hs-cTnT criteria was for CP: 68% 95% CI 96.6 to 99.4%) and for CP: 68% 95% CI 97.9 to 99.9%). As a score of one late presenters had a GRACE Score ≥ 140 and were not discharged. At 3 hours when the troponin became available after one hour, the NPV increased to 99.2%.

Conclusion: Using a high sensitive assay for troponin T, the novel ESC guidelines provide an effective way of rapid rule-out of NSTEMI with a very high however not perfect negative predictive value. These results indicate some room for further improvement of the algorithm.
recommendations on secondary prevention (9 studies) and pharmacological inter-
terventions (29 studies) were based on the largest amount of non-gov./industry
sponsorship (100% and 93%), compared with bleeding complications (9 studies) and
risk stratification (14 [a level of 0.05]) (76%, and 84%, respectively) (7) (6). Risk
stratification vs. pharmacological intervention. There were no categories of rec-
Recommendations that relied on a majority of studies funded by gov./

Conclusions: Based on this categorization, it appears that the funding for the ma-

Figure 1. FFR in acute phase of NSTEMI

Figure 1. FFR in acute phase of NSTEMI

Conclusions: These data are consistent with the hypothesis that active vascon-

Place: of active coronary vasocostriction in patients

Role of active coronary vasocostriction in patients

with NSTEMI

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Monasterio Foundation-CNR Region Toscana, MRI Laboratory.
Institute of Clinical Physiology, Pisa, Italy

Objective: We designed a study to evaluate the role of coronary vasocostriction in
precipitating non ST-elevation myocardial infarction in patients presenting at
with a significant coronary obstructive lesion.

Methods: We enrolled consecutive patients admitted for non-STEMI, and pre-

Results: We included 25 consecutive pts (63±11 year old; 20 males). At quan-
titative coronary angiography the diameter reduction of the culprit stenosis was
77±8% and the transtenotic pressure gradient of the culprit lesion was 30.4±5.4
mmHg. The Fractional Flow Reserve (FFR) was 0.63±0.13 and the Coronary
Flow Reserve (CFR) was 2.26±1.3. Following intracoronary nitrates, the pres-
ure gradient across the stenosis decreased to 14.0±5.8 mmHg (p=0.001). FFR
improved to 0.82±0.11 (p<0.0001), and CFR was 2.52±1.1 (p<0.05). In 18 patients
of the 25 (72%), FFR crossed the 0.75 threshold level and normalized after intra-
coronary administration of nitrates.

P5059

Increased sensitivity of troponin T in the early
diagnosis of non-ST-elevation myocardial infarction in
elderly patients presenting to an emergency department

P. Bahmann1, A. Bahmann2, M. Christ3, T. Bertsch4, C.C. Sieber1, 
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Germany; 2Department of Cardiology, Friedrich-Alexander-University, Erlangen,
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Purpose: Age >65 years has been reported to be the dominant factor associ-
ated with elevated high-sensitivity troponin T (hs-cTnT) levels in emergency room
(ER) patients. We hypothesized that a protocol implementing a serial hs-cTnT
measurement on admission and after 3 hours - as proposed by the latest ESC
guidelines - could be beneficial in the rapid rule-out of non-ST-elevation myocar-
dial infarction (NSTEMI) in the elderly. Therefore, we examined the accuracy of
hs-cTnT for an early diagnosis of NSTEMI in elderly patients presenting to our
ER.

Methods: During a 6-month period, we included all consecutive patients pre-

Results: Among 307 recruited patients (mean age 81±6 years), 206 (67%) pa-
thient had elevated hs-cTnT levels ≥0.014 μg/L. 45 (15%) of all patients had a

Baseline cTnI levels were higher in patients with AMI

Both groups (4.1 vs. 4.7 h, p=0.06). 36% of non-ACS-patients had heart failure,
20% rhythm disorders, 19% severe renal insufficiency, 11% hypertensive heart
disease, 6% valve disease, 4% endo-myocarditis and 4% sepsis. Using hs-cTnT
levels obtained at 3 hours after admission, the sensitivity was 93.6% and the
negative predictive value was 97.1% in rule-out NSTEMI. The diagnostic perfor-

Figure 1. FFR in acute phase of NSTEMI

Conclusions: These data are consistent with the hypothesis that active vascon-
strictor contributions to the cardiac coronary to the level of the culprit lesion in
ACS (non-STEMI) patients.

Release kinetics of cardiac biomarkers in patients
with acute myocardial infarction

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Purpose: High sensitivity cardiac troponin T (hs-cTnT) assays have been shown to

Methods: We analyzed the release kinetics of cTnT measured by the 4th gen-
eration and high-sensitivity assays in patients with HOMC undergoing TASH, as
a method uniquely proving earlier evidence of myocardial injury compared to the
4th generation cTnT assay and CKMB.

Results: After TASH all patients had elevated hs-cTnT levels

Direct comparison of absolute and relative changes in
high-sensitive cardiac troponin I in the early
diagnosis of AMI

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Background: The current guidelines for the diagnosis of acute myocardial infarc-
tion (AMI) require, especially in non-ST-elevation infarction, a rise and/or fall in
the levels of cardiac troponin (cTn). We evaluated whether absolute or relative
changes in high-sensitive cTn have a higher diagnostic accuracy.

Methods: In a prospective, observational, multicenter study, we analysed the di-
agnostic performance of absolute and relative changes in high-sensitive cTn as
measured with a novel pre-commercial prototype assay (Siemens: L00 0.5ng/L,
99th percentile 9ng/L and <100% CV at 3ng/L) in 1127 patients presenting to
the emergency department with symptoms suggestive of AMI. Blood samples were
collected at presentation and after 1, 2, 3 and 6 hours in a blinded fashion.
The final diagnosis was adjudicated by two independent cardiologists using all available medical

Results: Baseline high-sensitive cTn levels were higher in patients with AMI
(16.4% of the cohort) than in patients with other diagnosis of chest pain (p<0.001).
The area under the receiver operating characteristic curve for diagnosing AMI was significantly higher for 1-, 2- and 3 hour absolute changes versus relative changes in hs-CrT (Delta abs: AUC 0.840 (95% CI 0.790-0.900), 0.863 (0.834-0.902), 0.866 (0.802-0.930), 0.866 (0.802-0.930) vs 0.711 (95% CI 0.667-0.754), 0.795 (0.709-0.800), 0.732 (0.672-0.792) and 0.744 (0.676-0.812); p < 0.001 for the comparison). The receiver operating characteristic curve-derived cutoff values for 1-, 2- and 6-hour absolute changes were 0.6, 0.7, 8.2 and 9.6ng/l, all near the 99th percentile of the hs-CrT assay. Absolute changes at 2 hour were superior to relative changes in patients with both low and elevated baseline troponin levels. Combining the baseline troponin I levels with absolute and relative changes in a logistic regression performed even better in diagnosing AMI for absolute changes (1h: AUC 0.921 vs 0.864, 2h: 0.919 vs 0.866, 3h: 0.923 vs 0.858, 6h: 0.922 vs 0.860; p<0.001 for all comparisons).

Conclusions: Absolute changes of high-sensitive CrT levels showed a significantly higher diagnostic accuracy for AMI than relative changes, and seem therefore superior in the interpretation of the changes of elevated troponin levels regarding AMI.

*Cardiac magnetic resonance tissue characterization in the acute and chronic phase of refractory Non-ST elevation myocardial infarction*

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Background: In ST elevation myocardial infarction cardiac magnetic resonance (CMR) tissue characterization has been described in details. However, little is known about the acute and chronic phase, microvascular obstruction (MVO), area at risk and papillary muscle involvement in the acute and chronic phases in Non-ST elevation myocardial infarction (NSTEMI). Aim of our prospective study was to evaluate and compare tissue characteristics in the acute and chronic NSTEMI.

Methods: Forty NSTEMI patients who were revascularized within 48 hours after admission due to ST-segment elevation were enrolled into this study. CMR at 1.5T (Philips Medical Systems) was performed within 3-5 days and 3 months after symptom start. Left ventricular volumes were calculated using a short axis cine stack. Area at risk was evaluated using a 3D T2-weighted sequence in the same contiguous short axis orientation. Ten minutes after application of 0.2 mmol/kg gadolinium-based contrast agent (Dotarem, Guerbet) a 3D late gadolinium enhancement (LGE) sequence in the same orientation for evaluation of infarct size, MVO and papillary muscle involvement.

Results: Median age of the patients was 62.5±12.9 years, N=9 (22.5%) were female. The area at risk as determined using a 2-standard deviation threshold was 29.1±20.4 g. LGE revealed a significantly larger infarct size in the acute in comparison to the chronic phase (22.5±17.7 vs. 15.9±13.9 g, p=0.0003). In 6 (15%) patients presence of papillary muscle involvement was detected which was associated with larger infarct size in comparison to patients without papillary muscle involvement (45.3±21.8 g vs 18.6±13.7 g, p=0.003). MVO could be visualized in 16 (40%) patients in the acute phase and in 7 (17.5%) after 3 months. MVO was significantly reduced at follow-up in comparison to baseline (0.2±0.6 g vs. 1.2±3.2 g, p=0.05) and was associated with larger infarct size (30.1±22.1 g vs. 17.5±12.5 g, p=0.025). Infarct size negatively correlated with increase of ejection fraction at follow-up (r=-0.56, p=0.0002).

Conclusion: CMR provides a lot of information about myocardial tissue characteristics in NSTEMI patients. MVO and papillary muscle involvement correlate with infarct size. Further studies are warranted to prove clinical significance of described characteristics.

*Changing patterns of in-hospital management of acute coronary syndromes in the United Kingdom 1998-2008*

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Purpose: The management of acute coronary syndromes (ACS) has changed over the last decade as new treatments have been introduced. We sought to find out how treatments have changed in the UK over the last decade and whether these reflect contemporary guidelines.

Methods: Patterns of treatment were identified for patients enrolled in three consecutive multi-centre UK registries (mid-year recruitment, number of patients); PRAXIS-UK (1998, n=939), PROMIS-UK (2004, n= 931) and EQUIP-ACS (2008, n=935). Our main outcomes of interest were patterns of treatment at discharge, rates of angiography and revascularisation.

Results: (1998-64 years), diabetes (~16%), and entry systolic blood pressure (~144mmHg) were similar in all three registries. However the proportion of men and those with hypertension rose over time, while prior MI decreased. PRAXIS-UK had 16% normal ECGs and 19.4% ST depression while EQUIP had 30% revascularisation of treated groups. Changes in treatment patterns from 1998 to 2008 were: Low molecular weight heparin use increased from 45% to 91% while unfractionated heparin fell from 34% to 4%. Troponin was analysed in 5% of patients in 1998 and 100% in 2008. Rates of in-hospital complications including death did not change significantly over time.

Conclusion: Major increases in the rate of use of evidence based treatments, measurement of troponin and coronary revascularisation for non ST elevation ACS have occurred in the UK mainly from 1998 to 2004 with modest changes from 2004 to 2008. The lack of change from 2004 to 2008 suggests that more needs to be done to ensure that ACS patients receive the best care in the UK.

*Complementary intravenous Enoxaparin during percutaneous coronary interventions and NSTE-ACS: Is it necessary?*


Objectives: To assess the incidence of thrombotic complications during percutaneous coronary intervention (PCI) in patients (p) with non-ST elevation acute coronary syndrome (NSTEACS) pretreated with subcutaneous (sc) enoxaparin (ENK) with two different anticoagulation strategies.

Methods and Results: We analysed two retrospective cohorts of patients with NSTEACS pretreated with sc ENK 1mg/kg and PCI performed within 6 hours after the last dose of ENK. Cohort (C1) includes 44p with additional doses of ENK during PCI from 05/2009 to 12/2010. Cohort (C2) includes 41p with additional doses of ENK at the beginning of ENK (p=0.858, 6h: 0.922 vs 0.806; p<0.001 for all comparisons).

Conclusions: Absolute changes of high-sensitive CrT levels showed a significantly higher diagnostic accuracy for AMI than relative changes, and seem therefore superior in the interpretation of the changes of elevated troponin levels regarding AMI.

*Early diagnosis of acute myocardial infarction in patients with kidney disease using more sensitive cardiac troponin assays*

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Purpose: The rapid and reliable diagnosis of acute myocardial infarction (AMI) is a major unmet clinical need, particularly 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 cTn in this high-risk subgroup.

Methods: We conducted an international multicenter study to examine the diagnostic accuracy of new, more sensitive cTn assays in 1291 consecutive patients presenting to the ED with symptoms suggestive of AMI, of whom 186 (14%) were known to have elevated levels of cardiac troponins (cTn) already in the absence of AMI, which may lead to a lower diagnostic value of cTn in this high-risk subgroup.

Results: AMI was the final diagnosis in 33% (n=61) of all KD-patients as compared to 17% in patients with normal kidney function (p<0.001). Among KD-patients, both in the C1- and C2-arms, the 99th percentile with hs-TnT in 67%, with Tnl-Ultra in 16% and Tnl Abbott in 12% in patients with KD the diagnostic accuracy at presentation, quantified by the area under the receiver-operator-characteristic curve (AUC), was significantly lower in patients with kidney dysfunction than in patients without KD (0.75 vs 0.858, 6h: 0.922 vs 0.806; p<0.001 for all comparisons).

Conclusions: A high incidence of thrombotic complications occurs during PCI performed within 6 hours after the last dose of sc ENK in patients with NSTEACS. The intravenous administration of an additional ENK bolus of 0.75mg/kg at the beginning of the PCI significantly reduces the incidence of such complications while AntiXa levels observed after this extra bolus are within the safety range reported in previous studies.
greater for the sensitive cTn-assays compared to the standard assay (AUC for hs-
TnT, 0.88; Tnl Ultra, 0.89; and Tnl Abbott, 0.89 vs. AUC for the standard assay, 0.83, p<0.05 for all comparisons). In patients presenting within three hours after the onset of chest pain, Tnl Ultra (AUC 0.90) and Tnl Abbott (AUC 0.85) were su-
perior to hs-TnT (AUC 0.82, p<0.05 and p=0.015 for comparisons, respectively) and TnT4 (AUC 0.73, p<0.01 for both comparisons), whereas hs-TnT no longer performed superior to TnT4 (p=0.07). Using the predefined 99th-percentile cutoff of the sensitive cTn-assays, specificity and diagnostic accuracy was significantly reduced in KD-patients compared to the subgroup with normal kidney function, whereas sensitivity remained similar.

Conclusions: Sensitive cTn-assays have high diagnostic accuracy also in KD and are superior to conventional cTn-assays. In addition, there seems to be a difference among the sensitive assays in the early presenters with a higher diag-
nostic accuracy of Tnl Ultra and Tnl Abbott as compared to hs-TnT. Mld elevations are common in non-AMI patients and test-specific optimal cut-off-levels tend to be higher in KD-patients than in patients with normal kidney function.

**Purpose:** Troponin is recommended as the preferred biomarker for the diagnosis and risk stratification of non-ST myocardial infarction (NSTEMI). Per definition, the diagnosis AMI requires not only a positive test result but also corresponding signs and symptoms. We analyzed the association of chief complaint, cardiac main hospital diagnoses and troponin testing in two large EDs over one year period to evaluate its use in Emergency Medicine.

**Methods:** Data of all 34,333 patients who presented to either one of the two EDs were retrieved from the hospital information system. The patient’s chief complaint was documented in the electronic ED form by the treating physician.

**Results:** Troponin testing was performed in 38.1% (n=13071) of all patients. Of these, 23.3% presented with chest pain, 10.4% with dyspnoea, 5.8% with abdom-
inal pain, 3.3% with headache. The vast majority (57.1%) presented without one of these pre-specified chief complaints. Of all patient tested, 10.4% had a positive test result at admission, of these 24.6% with chest pain, 22.1% with dyspnoea, 2.5% with abdominal pain, 0.6% with headache and 50.2% with none of these symptoms. Even though 52.3% had a cardiac main hospital diagnosis, only 4.6% were diagnosed with a NSTEMI and 2.5% with a STEM1.

**Conclusions:** Troponin testing in internal emergency medicine

**Figure 1. Receiver operator characteristic curve**

**Conclusions:** The diagnostic accuracy of novel biomarkers of myocar-
dial injury in the unselected emergency room population

**Purpose:** Many patients with suspected non-ST-elevation acute coronary syn-
drome (NSTE-ACS) do not have significant coronary artery disease. Current diag-
nostic approach with repeated ECG and cardiac biomarkers requires observation

for ≈6-12 hours. The aim of this study was to investigate whether global strain by echocardiography measured at admission may exclude high-grade (>75%) coro-
nary artery stenosis in patients presenting with inconclusive ECG and normal cardiac biomarkers.

**Methods:** Patients with suspected NSTE-ACS were consecutively enrolled. 12-
lead ECG, Troponin T assay and echocardiography were performed on admis-
sion. Patients underwent coronary angiography after 24-72 hours. Conclusive ECG was ≥1 mm ST-segment change in any lead and Troponin T >0.03 μg/L was considered abnormal. Global peak systolic longitudinal strain (GLS) was mea-
sured using speckle tracking echocardiography in the 3 apical image planes and calculated from a 16 segment model.

**Results:** Out of 134 patients admitted with suspected NSTE-ACS, 41 patients presented without known coronary artery disease, inconclusive ECG and Tro-
ponin T <0.03 μg/L. GLS was ≥-15% in those with high-grade stenosis (n=22) and ≥-22% in those without high-grade stenosis (n=19). In a receiver operator-
characteristic curve analysis, GLS (AUC=0.95) was significantly better than both WMSI (AUC=0.72) and EF (AUC=0.65) at discriminating between no high-grade and high-grade coronary artery stenosis (p<0.01). A GLS of <20% excluded high-grade coronary artery stenotyes with 90% sensitivity and 96% specificity.

**Conclusions:** Myocardial strain by echocardiography is an accurate and easily available tool to exclude high-grade coronary artery stenosis among patients with suspected NSTE-ACS with inconclusive ECG and normal initial cardiac biomark-
ers.

**Figure 1. Positive and negative troponin results**

**Early strain echocardiography may exclude high-grade coronary artery stenosis in suspected non-ST-elevation acute coronary syndrome**

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**Conclusions:** Myocardial strain by echocardiography is an accurate and easily available tool to exclude high-grade coronary artery stenosis among patients with suspected NSTE-ACS with inconclusive ECG and normal initial cardiac biomark-
ers.

**Figure 1. Receiver operator characteristic curve**

**The diagnostic accuracy of novel biomarkers of myocardial injury in the unselected emergency room population**

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**Objective:** To examine the diagnostic accuracy of novel biomarkers of myocardial injury compared to highly sensitive troponin assays for the diagnosis of myocar-
dial infarction using the universal definition of myocardial infarction.

**Methods:** The study was a sub study of the point of care arm of the RATPAC trial (Randomised Assessment of Treatment using Panel Assay of Cardiac mark-
ers), set in the emergency departments of six hospitals. Prospective admissions with chest pain and a non-diagnostic echocardiogram were randomised to point of care assessment or conventional management. Blood samples were taken on admission and 90 minutes from admission for measurement of a panel of cardiac markers. An additional blood sample was taken at admission and 90 minutes from admission, separated and the serum stored frozen until subsequent analy-
ysis. Samples were analysed for high sensitivity cardiac troponin I (cTnI) by the Stratus CS (CS) for cardiac troponin T (cTnT) by the Roche high sensitivity car-
diac troponin T assay, for heart fatty acid binding protein (hFABP) and copeptin. Diagnostic accuracy was compared by construction of receiver operator character-
istic curves against the universal definition of myocardial infarction utilising standard laboratory measurements of cardiac troponin performed at the participating sites together with measurements performed in a core laboratory.

**Results:** Admission samples were available from 838/1132 patients enrolled in the study. There were 66 patients with a final diagnosis of myocardial infarction. Areas under the curve were as follows (confidence intervals in parentheses) cTnI CS 0.94 (0.90 - 0.98), cTnT 0.92 (0.88 - 0.96), FABP 1.04 (0.77 - 0.90) copeptin 0.62 (0.57 - 0.68).

Both hFABP and copeptin were diagnostically inferior to troponin. The combina-
tion of hFABP (at the 95th percentile) and either troponin (at the 99th percentile) increased diagnostic sensitivity, cTnI CS P 0.794 (0.673-0.888) to cTnI CS + hFABP 0.921 (0.824-0.974), cTnT 0.778 (0.655-0.873) to cTnT + hFABP 0.857 (0.746-
0.933) with a small loss in specificity, cTnI CS from 0.980 (0.967-0.989) to 0.923 (0.901-0.941) cTnT from 0.962 (0.946-0.975) to 0.916 (0.894-0.935). Addition of Copeptin (from an optimised decision level) increased sensitivity for cTnI CS to 0.905 (0.804-0.964) but reduced specificity to 0.591 (0.555-0.626) and for cTnT to 0.841 (0.727-0.921) but reduced specificity to 0.596 (0.561-0.631).

**Conclusions:** Additional measurement of copeptin is not useful in the chest pain population. Simultaneous measurement of hFABP improves sensitivity.
Reduction of medical consumption in low risk chest pain patients

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Background: Patients with chest pain are often admitted for clinical observation, and treated as ACS awaiting final diagnosis. Consequently, unnecessary diagnostics and treatment are common. The HEART score serves the making of a quick diagnosis and consists of five elements: History, ECG, Age, Risk factors and Troponin.

Accurate risk stratification of chest pain patients in the emergency department (ED) by means of the HEART score may help to identify low risk patients, defined by HEARTscore ≤3, who do not need additional work-up or hospitalization.

Methods: This study was performed in 260 patients in three hospitals in the Netherlands. These patients were part of a prospective validation study of the HEART score in 2388 chest pain patients in the ED of ten hospitals. Numbers of hospitalization days, exercise tests, echocardiography and various other examinations were counted.

Results: Chest pain patients visiting the ED were classified as low-risk, based on the HEART score, in 102/280 (36.5%) of the cases. MACE did not occur in these 102 patients; the risk of MACE was 15/870 (1.7%) in the low HEART score group of the entire prospective study. Eighteen patients (17.6%) were hospitalized for a total of 28 days and additional cardiology work-up was done in 52 patients (51%). Numbers of examinations were: 27 (28.5%) exercise tests, 16 (15.7%) echocardiograms, 5 (5%) CT scans and 6 (5.9%) PESCT.

Conclusion: When a policy would be made to withhold redundant medicine in low-risk chest pain patients, with a HEART score ≤3, hospitalizations would be saved in one fifth and various examinations in half of the patients. Improved risk stratification in chest pain patients may result in a reduction of medical consumption.

A significant proportion of patients with acute coronary occlusion lack ST elevation: Implications for diagnosis and provision of primary angioplasty services

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Purpose: Primary percutaneous coronary intervention (PCI) programmes vary in admission criteria from autonomous diagnosis with open access, to strict acceptance of ECG protocol positive (ST elevation or LBBB) cases. Rigid referral criteria may result in patients with acute coronary occlusions not receiving reperfusion therapy. We compared rates of coronary occlusion between ECG protocol negative and protocol positive cases in a cohort taken from our open access PCI service.

Methods: Presenting ECG, baseline characteristics, TIMI flow grades, peak creatine kinase levels, and mortality from 308 consecutive PCI cases performed from a cohort of 513 activations of the PCI programme (PPCI rate 60%) during 2008 were reviewed. Patients were categorised according to the presenting ECG:

- Group A: ST elevation 3mm or 1mm in two contiguous chest or limb leads respectively.
- Group B: Protocol positive (ST elevation or LBBB).
- Group C: Schaeremic changes displaying either ST segment depression or T-wave inversion, or group C: minor changes/within normal limits.

Results: 216 (70%) cases were in group A, with 46 (15%) in group B, and 46 (15%) in group C. Prevalence of TIMI 0/1 flow was 75% for group A patients vs. 74% for group B (P=0.93), and 63% for group C (P=11). Median Peak CK rise was higher in group A than group C (9400 IU/L vs 571 IU/L, P<0.01), but was similar to group B (9400 IU/L vs 925 IU/L, P=0.28). Age, vessel treated, and mortality are shown in the table. Cardiovascular risk factor prevalence did not differ between groups.

Conclusion: A significant minority of ECG protocol negative cases were found to have an acute vessel occlusion with comparable biomarker rises to the protocol positive group suggesting significant myocardial infarction.

Risk stratification in non-ST-elevation Acute Coronary Syndromes: utility of both GRACE and CRUSADE models

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Background: According to ESC guidelines, patients (pts) presenting with non-ST-elevation acute coronary syndromes (NSTE-ACS) should have their prognostic and bleeding risk determined using established risk scores (RS), namely GRACE for in-hospital mortality and ischemic events and CRUSADE RS for bleeding. However, the clinical implications and utility of combining both risk scores is less well established.

Aim: Evaluate how risk stratification combining GRACE and CRUSADE performs in pts with NSTE-ACS

Methods: Analysed 1425 pts (66±13 years, 72% male) with NSTE-ACS, prospectively included in a nationwide registry. GRACE RS and CRUSADE RS at hospital admission were calculated for each patient and tested, respectively, for p<0.001 for trend of CRUSADE risk in each strata of GRACE. p<0.001 for trend of overall CRUSADE AND GRACE risk.
predicting in-hospital death and major bleeding (defined using CRUSADE criteria). Pts were divided according to low, intermediate or high risk of fatal events, using GRACE RS (≤108, 109-140 or >140, respectively) and then sub-stratified into low, intermediate or high risk of major bleeding, according to CRUSADE RS (≤31, 31-40 or >40, respectively). In-hospital pharmacological treatment, procedures and events were compared between groups.

Results: GRACE and CRUSADE had a good performance in predicting in-hospital death (AUC 0.880, p<0.001) and major bleeding (AUC 0.755, p<0.001), respectively. Only 53% of pts had a concordant risk by both RS (table). Sub-stratification using CRUSADE was useful for identifying major bleeding risk across all categories of GRACE RS. Use of ibi/ili inhibitors, fondaparinux and radial access for catheterization diminished with increasing bleeding risk (p<0.001).

Conclusion: Both GRACE and CRUSADE RS have good performance for predicting in-hospital death and major bleeding, respectively. Half of NSTE-ACS pts have a discordant fatal and bleeding risk. CRUSADE RS can be used for identifying pts at risk of bleeding events, independently of risk estimated with GRACE RS.

P5072 Rapid rule-out of NSTEMI by using a high sensitive prototype assay for troponin I: a prospective evaluation of the safety of the novel ESC 2011 guidelines

Purpose: High-sensitive cardiac troponin (hs-cTn) assays have been shown to significantly improve the early diagnosis of acute myocardial infarction. The novel 2011 ESC guidelines for the management of acute coronary syndromes in patients without persistent ST-segment elevation contain for the first time a new fast track rule-out protocol including hs-cTn. We intended to verify the safety of this fast track protocol in our prospective study setting.

Methods: Out of our ongoing prospective international multicenter study 1102 consecutive patients who presented with symptoms suggestive of acute myocardial infarction and absence of significant ST-elevations in the ECG were included. The final diagnosis was adjudicated by two independent cardiologists using all available informations including high sensitive cardiac Troponin T (Roche). We examined the diagnostic accuracy of the novel ESC rapid rule-out protocol using the pre-commercial Beckman Coulter high sensitive cardiac troponin I assay (hs-cTnI, 99th percentile defined as 9.2 ng/l) performed on blood samples obtained in the emergency department at presentation and after 3 hours according to the novel guidelines. All patients were divided in line with the ESC algorithm into the subgroups of late presenters with chest pain onset/maximum (CPM) ≤ 6 hours and early presenters with CPM > 6 hours. In the former group, rapid rule-out was based on a single measurement using hs-cTnI and in the latter group, on two hs-cTnI values, at presentation and at 3 hours.

Results: Of all late presenters (n=393), 17% (n=67) received the final diagnosis of NSTEMI, compared to 15% (n=104) of early presenters (n=709). Three late presenters and three early presenters with the final diagnosis of NSTEMI had hs-cTnI levels below the cutoff of 9.2 ng/l. The overall negative predictive value (NPV) approaching only the hs-cTnI criteria was for CPM ≤ 6h 98.7% (95% CI 96.3 to 99.7%) and for CPM > 6h 98.7% (95% CI 96.3 to 99.7%). All missed patients had a GRACE Score below 140. As two late and two early presenters were not free of symptoms at the point of time when the decisive troponin became available, the NPV increased to 99.6% in both subgroups.

Conclusions: Using a novel high sensitive prototype assay for troponin I, the 2011 ESC guidelines provide an effective way of rapid rule-out of NSTEMI with a very high however not perfect negative predictive value. (ClinicalTrials.gov number, NCT00470587)

P5073 The nature and clinical outcomes of total occlusion in non-ST-elevation myocardial infarction; is it bad or good?
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Background and Objectives: Non-ST-elevation MI is a different disease entity from ST-elevation MI. While undergoing coronary angiography, there are lesions in NSTEMI with TIMI grade 0, showing near total occlusion. Our objectives are to get a knowledge in these situations.

Subjects and Methods: In 2011, 5694 patients were registered in COREA-AMI (Convergent REGistry of Atherosclerotic and chronAm university for AMI) registry. 2324 patients were NSTEMI, and we divided these patients into two groups, based on TIMI flow. Occluded lesion was defined as a lesion with 100% stenosis, or if TIMI flow 0.1, 1009 patients had occluded lesion, and 1315 patients had non-occluded lesion. We compared baseline characteristics, EG findings, in-hospital treatment, and long-term outcomes between patients with and without occluded culprit arteries.

Results: In baseline characteristics, initial creatine level, peak troponin before PCI, initial ejection fraction in echocardiography, total stent length, follow-up hsCRP showed significant difference between two groups. Also former as-priori, statin, metformin use was different between two groups. Total occlusion in NSTEMI was frequent in left circumflex artery. Using multivariate cox-regression analysis, the hazard ratio for occluded infarct artery was 1.67 (95% confidence interval 1.30-2.10, p=0.001). Kaplan-Meier curve for median follow-up of 36 months showed a significant difference between occluded and non-occluded lesion group.

P5074 One-year risk of stroke following acute myocardial infarction
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Background: Ischaemic stroke following acute myocardial infarction (AMI) is an important complication. It is unknown whether the risk has changed as the treatment of AMI has improved during the last decade, particularly in terms of antithrombotic, lipid lowering and reperfusion treatment. There is also conflicting data about predictors of stroke risk.

Objective: To obtain the one-year incidence of stroke following AMI, the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) database for the years 1998 to 2008 was merged with the Swedish National Patient Register (PAMR). The time period was divided by studying the entire time period into five separate periods. Independent predictors were identified using a multivariable Cox proportional hazards regression model.

Results: Between 1998 and 2008, 7108 out of 173233 patients with AMI suffered an ischaemic stroke within one year (4.1%). The years 2007/2008 were associated with a 21% relative risk reduction, compared to the years 1998-2000, relative risk (RR) 0.79 (95% CI 0.73-0.85), p<0.001. A reduced risk of stroke was also found for the years 2003/2004 and 2005-2006, compared to 1998-2000, RR 0.86 (95% CI 0.80-0.93), p<0.001, and 0.81 (95% CI 0.75-0.88), p<0.001, respectively.

Independent predictors of stroke were age, female sex, STEMI, prior stroke, prior diabetes mellitus, heart failure at admission and atrial fibrillation. Reperfusion treatment with fibrinolysis and PCI and treatment with aspirin, P2Y12-inhibitors and statins predicted a reduced risk of stroke.

Conclusions: The risk of ischaemic stroke within a year following myocardial infarction is substantial but has clearly been reduced during the studied time period. The predictive factors found correlate well with previous investigations. Reperfusion treatment, thrombocyte aggregation inhibition and lipid lowering are the main contributors to the observed risk reduction.

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Purpose: Recent evidence suggests improvements in provider care for acute myocardial infarction (AMI) and significant reductions in in-hospital mortality across

```sql
SELECT * FROM table_name WHERE column = 'value';
```
all age groups. We investigate whether the impact of temporal advances in card-
diac care for the elderly with AMI extend beyond the hospital stay.

Methods: A mixed-effects regression analysis of the Myocardial Ischemia Na-
tional Audit Project (MINAP) was performed stratified by STEMI/NSTEMI, sex,
and age group on 30-day mortality and opportunity-based composite scores
(OBCS) for aspirin, ACE-inhibitor, statin, β-blocker, and referral for cardiac reha-
bilitation for 476342 patients with AMI between 2004 and 2009 from 215 hospitals
in England and Wales.

Results: From 2004 to 2009 30-day mortality rates (95% CI) decreased: STEMI: 2004/5: 12.0% (11.7 to 12.5%); 2006/7: 10.8 (10.6 to 11.1%); 2008/9: 9.6 (9.4 to
9.9); NSTEMI: 2004/5:10.1 (9.9 to 10.3); 2006/7: 8.8% (8.6 to 9.0%); 2008/9:
7.8% (7.7 to 8.0%). The proportion of patients with AMI achieving an OBCS >80%
increased over time. 2004/5: 84.0%, 2006/7: 90.0%, 2008/9: 93.2%, P<0.001.
The proportion of patients achieving an OBCS >80% was lower in females than
males (P<0.001), and decreased with increasing age group for STEMI (P<0.001)
and NSTEMI (P<0.001). Of patients ≥80 years, only females with STEMI did not
show a significant reduction in 30-day mortality risk. Male STEMI and NSTEMI
demonstrated significant reductions in 30-day mortality risk, except STEMI aged
≥65 years. For females, the only group to demonstrate a significant reduction in
30-day mortality risk were those aged ≥80 years with NSTEMI.

Conclusions: In England and Wales, for patients hospitalized with AMI there are
sex- and age-dependent differences in temporal improvements in 30-day mortality
rates. The proportion of patients with an OBCS >80% compared with in-hospital mortality, equivalent temporal improvements in mortality do not appear to extend
beyond the hospital stay for all groups of patients.

P5076 The rs12526453 polymorphism in intron of the PHACTR1 gene is associated with 5-year mortality of patients with ST-elevation myocardial infarction
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Purpose: The rs12526453 (C/G) is a single nucleotide polymorphism in intron of
the PHACTR1 gene (phosphatase and actin regulator 1). It was shown to be asso-
ciated with early-onset myocardial infarction in a genome-wide association study
with cytosine as a risk allele (1). The mechanism, however, remains unknown.

Methods: We included in our registry consecutive patients with STEMI treated
with primary PCI who survived 48 hours from hospital admission. Genotyping
was performed with a TaqMan SNP Genotyping Assay using the ABI 7500 Real
Time PCR System (Applied Biosystems). The analyzed end-point was total 5-year
mortality. The genotypes were: CC, CG and GG.

Results: The study group comprised 629 patients (mean age 62±12 years; 25%
of females, n=157; TIMI 3 obtained in 93.1% of patients, n=586). The per-
centages of CC, CG and GG genotypes were: 10% (n=63), 44.7% (n=261) and
45.3% (n=285), consecutively. No significant differences in clinical characteris-
tics were found between the genotypes. The 5-year total mortality was 16.2% (n=102). There died 28.5% (n=18) of CC high-risk homoyzogotes, 16.4% (n=44) of
heterozyzogtes and 13.3% (n=38) of GG homoyzogtes (Figure 1). The difference
was statistically significant (p<0.009, log-rank test).

Conclusions: The CC genotype of the rs12526453 polymorphism in intron of the
PHACTR1 gene is associated with increased 5-year mortality in patients with
STEMI treated invasively.


P5077 High 3-year-mortality rates in females with newly diagnosed diabetes after acute STEMI and NSTEMI in clinical practice in Germany: results of the Sweetheart-register
Heidelberg, Germany; 2Herzzentrum Ludwigshafen am Rhein, Germany; 3Herzzentrum Ludwigshafen, Ludwigsheim, Germany

Background: Many patients with coronary artery disease suffer from diabetes
to its pre-states. Joint guidelines by the ESC and the EASO recommend testing
for diabetes using OGTT in patients with established CAD and without previously
known diabetes.

Methods: Since 2007, 2,767 consecutive patients with STEMI or NSTEMI
were enrolled into the MI-registry SWEETHEART to identify abnormal glucose
metabolism and to document acute treatment and outcome. In patients with pre-
viously unknown diabetes, oral glucose tolerance test (OGTT) was performed
at day 4 after acute MI. We examined gender differences in the prevalence of
abnormal glucose metabolism and the impact of newly diagnosed diabetes on
3-year-mortality of MI.

Results: Female patients with MI were older, less often had prior MI and prior
PCI as compared to males. Female patients had a higher rate of known diabetes
as well as a longer duration of diabetes at the time of MI. The prevalence of
newly diagnosed impaired glucose metabolism was much higher in females than
in males. In females, OGTT identified another 19.8% with manifest diabetes and
18.1% with impaired glucose tolerance (IGT)/impaired fasting glucose (IFG) as
compared to 15.3% and 23.3% in males respectively. After 3 years of follow up,
female patients with newly diagnosed diabetes had a 30.5% mortality similar to
that of females with already known diabetes (30.0%).

Conclusion: Although the prevalence of known diabetes was already much
higher in females, the rate of newly diagnosed diabetes was significantly in-
creased in females as compared to males. Females with newly diagnosed di-
betes had the same 3-year mortality as those high risk patients with MI and
already known diabetes.

P5078 The clinical significance of right ventricular
dysfunction with or without pulmonary hypertension
after acute myocardial infarction
D. Aronson, K. Shahar, H. Hammerman, R. Dragu. Rambam Health Care Campus, Haifa, Israel

Background: Right ventricular (RV) dysfunction may accompany inferior wall
infarction and is not uncommon in patients with acute anterior infarction. Pulmonary
hypertension (PH) may exacerbate RV dysfunction (RVD). However, with severe
RVD, pulmonary arterial pressure may decrease as a consequence of low RV
output. We sought to determine the prognostic implications of RVD in relation to
PH in acute myocardial infarction (AMI).

Methods: Echocardiography was performed in 1054 patients with AMI. RV func-
tion was assessed both visually and by measuring the RV fractional area change
(RV-FACT). Patients were classified into 4 groups according to the presence or ab-
sence of pulmonary hypertension (estimated pulmonary artery systolic pressure
>35 mmHg by echocardiography) and RV (RV-FACT>35%). The primary end-
point was all-cause mortality with a mean follow-up of 3 years.

Results: RV was present in 141 patients, with 91 (6.6%) and 50 (4.7%) patients
with and without PH, respectively. With patients with RVD without PH, patients
with RVD and PH presented with higher Killip class (Killip class II or
higher: 48% vs. 14%, P<0.01) and were more likely to have reduced left ven-
tricular (LV) systolic function (LV ejection fraction<45%: 71% vs. 44%, P<0.01).

Figure 1. 5-year survival for specific genotypes

Conclusion: The prevalence of known diabetes was already much
higher in females, and the rate of newly diagnosed diabetes was significantly in-
creased in females as compared to males. Females with newly diagnosed di-
betes had the same 3-year mortality as those high risk patients with MI and
already known diabetes.
The results of a multivariable Cox regression model are shown in the Figure. Patients with RVD and normal pulmonary pressures had the highest adjusted risk for mortality.

**Conclusion:** Patients with RVD without PH are at a particularly high risk for mortality despite better LV systolic function. These results emphasize the importance of interpreting RV function in combination with pulmonary pressures data.

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**P5079 One year outcome in HIV-infected patients with myocardial infarction**

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**Background:** Risk of myocardial infarction (MI) in HIV infected patients is increased and short term prognosis is good. One year outcome remain to be determined in large scale study.

**Methods:** From the French nationwide hospital medical information database, all the consecutive patients hospitalized in the 1546 French hospital/clinics for myocardial infarction from 1st January 2005 to 31st December 2009 were included. We compared one year outcome between patients infected or not by HIV.

**Results:** Among the 628454 patients included, 1286 (0.2%) was infected by HIV. At one year of follow-up, we observed an increased rate of recurrent MI in HIV-infected patients than non-infected patients (14.9% vs 11.3%; p=0.02) and respectively 14.3% vs 12.9%; p=0.02) and relatively 14.9% vs 11.3% (p=0.01) in a sub-group of patients matched for age, sex and type of MI (ratio 1:2).

**Conclusion:** One year outcome in HIV-infected patients with myocardial infarction is increased and is associated with a higher recurrent MI rate compared to non-infected patients.

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**P5080 Accuracy of high-sensitive cardiac troponins for long-term mortality**

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**Background:** Several high-sensitive cardiac troponins (hs-cTn) have recently been introduced. It is unknown whether hs-cTn is most accurate for long-term prognosis and whether early changes improve prognostic accuracy.

**Methods:** In a prospective, international multicenter study, hs-cTn was measured with three assays (hs-cTnT, Roche Diagnostics; hs-cTnI, Beckman-Coulter; hs-cTnl, Siemens) in a blinded fashion at presentation and 1 hour later in 849 unselected patients with acute chest pain. Patients were followed-up 2 years regarding mortality.

**Results:** Acute myocardial infarction was the adjudicated final diagnosis in 150 (17.7%) patients. 62 (7.3%) patients died during the first 2 years. The prognostic accuracy of hs-cTnT (Roche Diagnostics) at presentation for mortality in the first 2 years as quantified by the area under the ROC curve (AUC) was 0.756 (95% CI 0.726-0.785) and outperformed both hs-cTnI (Beckmann-Coulter) 0.704 (95% CI 0.672-0.734; p=0.029 for comparison) and hs-cTnl (Siemens) 0.687 (95% CI 0.653-0.718; p=0.010 for comparison) (Figure 1). Absolute changes in the first hour of hs-cTnT were more accurate than relative changes (AUC 0.660; 95% CI 0.627-0.692 vs. 0.512; 95% CI 0.477-0.548; p=0.035 for comparison) (Figure 2). Combining presentation values of hs-cTnT in the first hour did not further improve their prognostic accuracy (AUC 0.747; 95% CI 0.717 to 0.776; p=0.064 for comparison).

**Conclusion:** Hs-cTnT seems to be more accurate than hs-cTnI in the prediction of long-term mortality. Absolute changes outperformed relative changes in the first hour as to long-term mortality in all three hs-cTn assays but were inferior to respective presentation values.

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**P5081 Large differences between patients with acute myocardial infarction included in two Swedish health registers**

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**Background:** Acute myocardial infarction (MI) is a leading cause for morbidity and mortality in Sweden. We aimed to compare patients with an acute MI included in the Register of information and knowledge about Swedish heart intensive care admissions (RIKS-HIA, now included in the register Swedeheart), and the Swedish statistics of acute myocardial infarctions (S-AMI).

**Methods:** Population based register study including RIKS-HIA, S-AMI, the National patient register and the Cause of death register. Odds ratios were determined by logistic regression analysis.

**Results:** From 2001 to 2007, 114 311 cases in RIKS-HIA and 198 693 cases in S-AMI were included with a discharge diagnosis of an acute MI. Linkage was possible for 110 958 cases. These cases were younger, more often males, had less concomitant diseases and were more often treated with invasive coronary artery procedures than patients included in S-AMI only. There were substantial regional differences in proportions of patients reported to RIKS-HIA.

**Conclusion:** Approximately half of all patients with an acute MI are included in RIKS-HIA. They represent a relatively more healthy population than patients included in S-AMI only. These limitations are important to know about since the register has become increasingly important in international research. S-AMI covers almost all patients with an acute MI but has limited information about the patients. Used in combination these two registers can give better prerequisites for improved quality of care of all patients with acute coronary syndromes.
**Non-ST-segment elevation acute coronary syndrome caused by the left main stem stenosis - impact of multivessel diseases on treatment strategy and 12-month. Analysis from the PL-ACS Registry**

M. Gierlok1, M. Gasiorek1, M. Hawranek1, M. Tajstraitra, P. Buszman2, J. Kubica3, A. Lekston1, M. Zembala1, G. Opolski4, L. Polonski1 on behalf of PL-ACS Investigators. 1Medical University of Silesia, Silesian Center for Heart Diseases (SDCH), Zabrze, Poland; 2American Heart of Poland, Katowice, Poland; 3Nicolaus Copernicus University, Collegium Medicum, Department of Cardiology, Bydgoszcz, Poland; 4Medical University of Warsaw, Warsaw, Poland

The aim was to analyze the impact of multivessel disease on 12-month mortality in patients with NSTE-ACS caused by LM stenosis. **Methods:** All patients with NSTE-ACS caused by LM stenosis registered in the PL-ACS between 10.2003 and 11.2009 were included. Patients were divided into 4 groups according to the number of significantly stenosed vessels. **Results (table):** In PL-ACS Registry 1654 (2.5%) pts from 65767 had NSTE-ACS caused by LM stenosis. As the number of stenosed vessels increased the percentage of pts treated by PCI decreased and by CABG raised. In-hospital and 12-month mortalities increased together with the number of stenosed vessels. **Conclusion:** Adjustment the number of significantly stenosed vessels remains significantly associated with higher 12-month mortality (relative risk = 1.14, 95% CI = 1.01-1.28). P<0.038.

**Table 1**

<table>
<thead>
<tr>
<th>Isolated LM stenosis</th>
<th>LM + 1 vessel</th>
<th>LM + 2 vessels</th>
<th>LM + 3 vessels</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>352 (21.3%)</td>
<td>341 (20.6%)</td>
<td>512 (31.0%)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>63±11.3</td>
<td>65±11.5</td>
<td>66±10.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>19.9</td>
<td>21.7</td>
<td>26.9</td>
<td>27.2</td>
</tr>
<tr>
<td>Prior PCI, %</td>
<td>14.5</td>
<td>25.2</td>
<td>26.9</td>
<td>33.0</td>
</tr>
<tr>
<td>Prior CABG, %</td>
<td>5.1</td>
<td>10.8</td>
<td>4.9</td>
<td>6.2</td>
</tr>
<tr>
<td>Cardiac arrest before admission, %</td>
<td>2.7</td>
<td>3.1</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Killip 3 or 4 on admission, %</td>
<td>4.5</td>
<td>4.7</td>
<td>8.4</td>
<td>8.7</td>
</tr>
<tr>
<td>In-hospital bypass surgery (CABG), %</td>
<td>6.0</td>
<td>9.1</td>
<td>11.1</td>
<td>10.5</td>
</tr>
<tr>
<td>In-hospital CABG after discharge, %</td>
<td>44.9</td>
<td>48.4</td>
<td>58.7</td>
<td>63.7</td>
</tr>
<tr>
<td>In-hospital mortality, %</td>
<td>5.1</td>
<td>5.3</td>
<td>5.2</td>
<td>5.7</td>
</tr>
<tr>
<td>In-hospital major bleeding, %</td>
<td>1.7</td>
<td>1.2</td>
<td>2.2</td>
<td>2.5</td>
</tr>
<tr>
<td>In-hospital re-infarction, %</td>
<td>1.4</td>
<td>1.2</td>
<td>1.2</td>
<td>2.9</td>
</tr>
<tr>
<td>In-hospital in-hospital mortality, %</td>
<td>4.3</td>
<td>2.6</td>
<td>5.9</td>
<td>8.4</td>
</tr>
<tr>
<td>12-month mortality, %</td>
<td>10.5</td>
<td>14.9</td>
<td>16.0</td>
<td>22.5</td>
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</tbody>
</table>

**Conclusion:** The implementation of this universal health plan in Chile was associated with an increase in 1-year survival in AMI patients. This has been achieved through a better use of evidence based medicine and reperfusion strategies. This effort has contributed to improving inequity in the health care attention of AMI patients.

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**Prognostic factors in chest pain patients: a quantitative analysis of the HEART score**

B.E. Backus1, A.J. Six2, P.A. Doevendans1, J.C. Kelder3, E.W. Steyerberg4, Y. Vergouwe4, 1University Medical Center Utrecht, Department of Cardiology, Utrecht, Netherlands; 2Zuwe Hoploot Hospital, Woerden, Netherlands; 3St Antonius Hospital, Department of Cardiology, Nieuwegein, Netherlands; 4Erasmus Medical Center, Rotterdam, Netherlands

**Purpose:** Risk stratification for chest pain patients at the emergency department is recommended in several guidelines. The HEART score is based on medical literature and expert opinion and calculates the risk of a major adverse cardiac event (MACE). We aimed to assess the predictive effects of the five HEART components and to compare performance of the original HEART score with a model based on regression analysis. **Methods and results:** We analyzed prospectively collected data from 2388 patients, of whom 407 (17%) had a MACE within 6 weeks (AMI, PCI, CABG, significant stenosis with conservative treatment and death due to any cause). Univariate regression analysis showed the same predictors as those used in the HEART score. An adjusted score was based on multivariable logistic regression analysis (HEART-adj), which showed slightly better calibration and discrimination than the HEART score (c-statistic HEART 0.83, HEART-adj 0.85). HEART-adj proved in a decision curve analysis to be clinically more useful than HEART for decision thresholds over 25% (figure 1). Nevertheless, the original HEART classified patients better than HEART-adj, when the previously defined thresholds of 2.5% and 40% were applied (NRI=14.1%).

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**Conclusion:** The implementation of this universal health plan in Chile was associated with an increase in 1-year survival in AMI patients. This has been achieved through a better use of evidence based medicine and reperfusion strategies. This effort has contributed to improving inequity in the health care attention of AMI patients.

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**Occurrence of major bleeding during long-term follow-up of unselected patients with STE vs NSTE acute coronary syndromes**


**Background:** The occurrence of bleeding following ACS has been well described in clinical trials but little is known in the real world, especially in the long-term. **Purpose:** To evaluate bleeding rates during long-term follow-up of a large, unselected ACS population with particular reference to comparison between STE and NSTE. **Methods and results:** 2046 consecutive patients hospitalized in 2004-2005 were followed up for 5 years after discharge. In-hospital bleeding was classified as major or minor according to TIMI classification. Major bleeding (MB) occurred after discharge was defined as follows: requiring transfusion or surgery or hospitalization, reduction in haemoglobin of more than 5 g/dl or intracranial haemorrhage. Events were adjudicated by the Endpoint Committee and disagreements resolved by consensus. **Results:** The mean age was 71.6 years. Patients with NSTE-ACS were older and had a higher prevalence of AF, Killip class III-IV and comorbidities compared to patients with STE-ACS. Patients in the latter group were more likely to be treated with GP IIb-IIIa Inhibitors and to receive both aspirin and P2Y12 inhibitor (82% vs 64%, p<0.001). PPCI was performed in 84% of STE-ACS and 70% of NSTE-ACS were managed invasively. Overall, during the 5 years of follow-up there were 135 MB with no significant difference between STE and NSTE-ACS in any time period (figure). Of these, only 30 took place during the index hospitalization, whereas 105 occurred after discharge, raising from 1.5% in-hospital to 3.5% at 1 year and 7.9% at 5 years.
Early mortality of acute coronary syndromes (ACS) has vastly declined thanks to interventional and pharmacological therapy. However, there is growing evidence of high events in the long run, but data are mainly derived from large clinical trials.

Objective: To compare 5-year outcome of unselected patients with STE versus NSTE ACS in a real-world context of contemporary acute treatment and secondary prevention.

Methods: All consecutive patients with ACS admitted in 2004-2005 were enrolled (896 STE, 1150 NSTE). Patients in the former group were younger, had fewer comorbidities and more often received antiplatelet therapy at discharge. In the whole population, about 23% had a composite endpoint of death, reinfarction, or stroke during 5 years of follow-up. Figure 1 shows the Kaplan-Meier curves up to 5 years. In the first 30 days, the mortality is higher for STE but curves intersect at 1 year and 5-year mortality tends to be higher for NSTE without statistical significance. Landmark analysis displays a greater risk for NSTE after the first year (STE vs NSTE HR=0.67; 95%CI 0.51-0.84, p=0.001).

Conclusion: Despite the extensive use of antithrombotic therapies and PCI, the rates of in-hospital MI are acceptably low in the real world and similar to those reported for trials of ACS. On the contrary, occurrence of MI is still high in the long run and greater than shown in trials.
**P5089** Pathological Q-wave development in myocardial infarction in patients treated by primary percutaneous coronary intervention

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**Background:** The criteria for pathological Q-waves after acute myocardial infarction (MI) have changed in recent years. Also, there is limited data regarding correlation of Q-wave regression and preservation of left ventricular fraction (LVEF) in patients with an initial Q-wave MI.

**Methods:** Standard 12 lead electrocardiogram (EGC) was recorded in 200 ST-elevated myocardial infarction (STEMI) patients treated with primary percutaneous coronary intervention. ECGs were recorded before and following PCI, as well as at 1, 4, 12 and 24 months of follow-up. Cardiac magnetic resonance imaging (CMR) examination was performed at 4±2 days after reperfusion and repeated after 4 and 24 months.

**Results:** The incidence of Q-wave MI according to the 2007 criteria was 58%, 1 hour after PCI. At 24 months of follow-up, 22% of patients with initial Q-wave MI displayed Q-wave regression. The “classic” ECG criteria showed strongest correlation with infarct size as measured by CMR. Patients with Q-wave MI had larger infarct size and lower LVEF on baseline CMR respectively (24±10% LV mass and 37±8% compared to patients with non-Q-wave MI (17±9% LV mass, p<0.01 and 45±8%, p<0.001). Patients with Q-wave regression displayed significantly larger LVEF improvement in 24 months (9±11%) as compared to both Q-wave MI (2±6%) as well as non-Q-wave MI (3±8%, p=0.04 for both comparisons).

**Conclusion:** Association of Q-waves with infarct size and LVEF is strongest when using the “classic” Q-wave criteria. Q-wave regression is associated with the largest improvement of LVEF over a 2 year follow-up.

**P5090** Long-term prognosis estimation after acute coronary syndrome: is there a role for angiographic scores?

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**Background:** Angiographic scores are useful tools to assess the severity of coronary lesions and can provide prognostic information. We aimed to explore the association of Leaman Score (LS) and Duke Jeopardy Score (DJS) with 10-year mortality, compared with Pts under the cut-off (Figure). Multivariable analysis revealed an independent association of LS with 10-year mortality (HR 1.14; p=0.65).

**Methods:** Retrospective analysis of consecutive Pts with ACS submitted to coronary angiography. Extension of coronary disease was calculated using LS and DJS. ROC-curves were performed to test sensitivity and specificity of the scores for the prediction of 10-year mortality. The area under the curve (AUC) and the better discriminatory value for the occurrence of this endpoint were determined for both scores, and Kaplan-Meier analysis was used to compare Pts with LS and DJS under and above the cut-off. A multivariable Cox regression analysis was performed to test the independent association of scores with mortality.

**Results:** Of the 662 Pts included (mean age 62±11 years, 80% male), 151 (22.8%) died. The mean values were 3.9±3.0 for LS and 2.6±2.0 for DJS. The AUC for LS was 0.61 (IC) and for DJS 0.58 (IC) with cut-off points of 2.0 and 4.0, respectively. Pts with LS and DJS over the cut-off presented significant increase in 10-year mortality, compared with Pts under the cut-off (Figure). Multivariable analysis revealed a significant independent association of LS with 10-year mortality (HR 1.06, 95%CI 1.01-1.12; p=0.018), not shown by the DJS (HR 1.03, 95%CI 0.92-1.14; p=0.65).

**Conclusions:** In this population of patients with ACS submitted to coronary angiography, both scores were associated with 10-year mortality in univariate analysis but only the Leaman score was an independent predictor of long-term mortality.

**P5091** Bleeding complications in patients with acute myocardial infarction. A gender perspective

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**Purpose:** During last years bleeding complications associated with acute myocardial infarction (AMI) has gained increased attention. Many, but not all, studies have shown a higher incidence in women. Furthermore bleedings has been shown to have a large impact on outcome. Whether there are gender differences in consequence of a bleeding complication is not well known.

**Methods:** From the Swedish national quality register, SWEDEHEART, we included 97862 cases diagnosed with AMI (35747 women and 62115 men). Between the year 2003 and 2009 with one year follow up. Major bleeding was defined as fatal, intracranial or Hemoglobin decrease with ≥50 g/L. Non-major bleeding was defined as a bleeding requiring transfusion or surgical intervention. We used chi square test and students t-test for statistical analyses with a significance level of p<0.05.

**Results:** Women were older (75 vs 69 y) and had more diabetes and hypertension, while men were more likely to be smokers or to have previous kidney disease. Men had more AMI in the history and also significantly more revascularization with either PCI or CABG.

Rates of severe bleedings were low, but higher in women (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No bleeding</td>
<td>98.3%</td>
<td>97.2%</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.3%</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td>Non-major bleeding</td>
<td>1.4%</td>
<td>2.3%</td>
<td></td>
</tr>
</tbody>
</table>

Non-bleeding women had significantly higher mortality than non-bleeding men, both short- and long-term mortality, 7.7 vs 5.2% (p<0.001) in 14 d and 19.9 vs 13.9% (p<0.001) in one y. Major bleeding had a high impact on outcome in both women and men regarding mortality at 14d (36.6% vs 42.9%, p=0.211) and 1y (46.2 vs 53.9%, p=0.021) but without difference between the genders. In patients with a bleeding complication requiring transfusion or surgery there was an indication of higher mortality in men at 14 d (11.4 vs 8.2, p<0.03) and at 1y (28.5 vs 24.6 p<0.08).
Conclusion: The major finding of this study is that women with AMI have a higher rate of bleeding complications than men. Even though women have an overall higher short-and-long-term mortality, among bleeding patients there is no difference between the genders or even higher mortality in men. Consequently, the prognostic impact of a bleeding complication appears higher in men.

P5092
Angiotensin receptor blockers as the first choice in patients with preserved left ventricular systolic function after acute myocardial infarction from the Korean Acute Myocardial Infarction Registry
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Purpose: It has not been known that the prognostic impact of angiotensin II receptor blockers (ARBs) compared with angiotensin-converting enzyme inhibitors (ACEIs) in reducing major adverse cardiovascular events (MACE) in patients with preserved left ventricular systolic function (LVFSF) after acute myocardial infarction (AMI).

Methods: Between November 2005 and January 2008, 5,012 ACEI- or ARB-naïve patients with preserved LVFSF (LV ejection fraction more than 40% by 2D echocardiogram) after AMI were included from the Korean AMI Registry. Patients who had already received ACEIs or ARBs before hospitalization were excluded from this study. The 12-month MACEs were defined as death and non-fatal MI. Results: The prescription rate of ARBs among these ACEI- or ARB-naïve patients (95%) is higher than ACEIs users (87%). Before propensity score (PS) matching, there were no significant differences in the 12-month MACEs (3.9% versus 3.6%, p = 0.664) and mortality (3.2% versus 3.0%, p = 0.810) between ACEIs use and ARBs use. For each patient, a PS indicating the likelihood of using ARBs during hospitalization or at discharge was calculated using a non-parsimonious multivariable logistic regression model, and was used to 1:3 match the patients on ARBs with the patients on ACEIs, leaving 594 ARBs users versus 1,782 ACEIs users. The 12-month MACEs and mortality were assessed using matched logistic and Cox regression models. Compared with ACEIs, the ARBs significantly reduced 12-month MACEs (2.7% versus 4.9%, hazard ratio [HR] 0.540; 95% confidence interval [CI] 0.317–0.920; p = 0.023) and mortality (2.0% versus 3.8%; HR 0.525, 95%CI 0.284–0.969; p = 0.039).

Conclusion: In real-world practice, the 12-month MACEs and mortality were significantly higher in ACEIs users as compared with ARBs users in patients with preserved LVFSF after AMI.

P5094
Copeptin predicts long-term mortality in patients with non-st-elevation myocardial infarction
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1Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany; 2Justus-Liebig University Giessen, Medical Clinic I, Cardiology, Giessen, Germany; 3Fritz-Groedel Institute of the Kerckhoff Clinic Heart & Thorax Center, Bad Nauheim, Germany

Purpose: Copeptin has been shown to improve diagnostic sensitivity when used in combination with conventional measured cardiac troponin T (cTnT) in patients with suspected acute coronary syndrome (ACS). However, less is known about the predictive value of differences in patients with and without acute myocardial infarction. Therefore, in the present study we aimed to analyse the possible predictive value of copeptin in patients with Non-ST-Elevation myocardial infarction (NSTEMI) and unstable angina (UA).

Methods: 321 patients with suspected Non-ST-elevation ACS (NSTEMI)-ACS) were included in the study. Final diagnosis of NSTEMI was made in 201 patients (62.6%), 107 patients (27.1%) had unstable angina pectoris (UA). The remaining 33 patients (10.3%) were without coronary artery disease (CAD) documented by coronary angiography. Copeptin was measured on admission. Blood was taken immediately after admission and was sent to the laboratory for centrifugation and frozen stored at –80°C until assayed.

Results: Copeptin plasma levels were higher in patients with NSTEMI compared to patients with UA (16.6 pmol/ml IQR [10.7-35.6] vs. 13.2 pmol/ml IQR [7.8-30.6]; P=0.019). There was no difference in copeptin plasma concentrations in patients with UA compared to patients without documented CAD (17.2 pmol/ml IQR [10.7-35.4] vs. 13.7 pmol/ml IQR [8.4-31.7]; P=0.08). During 5-year follow up, 29 (14.4%) patients with NSTEMI and 6 (9.0%) patients with UA and 3 (9.0%) patients without CAD died. The mortality rate among patients with NSTEMI and copeptin plasma concentration ≥ 14.0 pmol/ml was higher during 5-year follow up (LogRank 12.1; P=0.01, multivariate Cox-regression 39% CI 1.003-1.023; P=0.01). Excluding patients with NSTEMI from the analyses mortality did not differ in patients with copeptin plasma concentration ≥ 14.0 pmol/ml compared to patients with copeptin levels <14.0 pmol/ml.

Conclusion: Copeptin has a predictive value for long-term mortality in patients with NSTEMI. However, this difference is restricted to patients with NSTEMI.

P5095
Prognostic implications of sleep duration in first months after ST-elevation myocardial infarction
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Purpose: Too little or too much sleep are associated with adverse health outcomes including: hypertension, type 2 diabetes, obesity and poor self-rated health. The aim of this study was to assess the relationship between duration of sleep and all-cause mortality in ST-elevation myocardial infarction (STEMI) patients.

Methods: 407 consecutive patients (271 males), aged 36 to 79 years (mean age, 59.4±10.6 years), admitted to our department with diagnosis of STEMI, were enrolled in the study within 12 hours from the onset of symptoms. All patients were asked by telephone for sleep duration in first 3 months after discharge from the hospital. The primary endpoint was all-cause mortality. Response rate (follow-up) was carried out as close to 2 years from the baseline interview. 28 patients were lost of follow-up and were not analyzed. Sleep duration was assessed by asking the study participants to give the habitual night sleep time: How many hours do you sleep usually each night? Patient response: |__|__| hours per night. According to the sleep duration, we divided patients into 3 groups: group A) the reference category was defined as 6-8 sleep hours per night, group B) short sleep was defined as < 6 hours per night and group C) long sleep was defined as > 8 hours per night.

Results: Out of total of 379 patients, 35 (9.2%) patients slept less than 6 hours and 15 (6.9%) patients slept more than 8 hours per night. Patients with longer sleep durations were older (62.5±10.2 vs. 58.8±10.6 years; p<0.01), had significant higher death rates (18% vs. 1.9%; p<0.0001), often history of diabetes mellitus (27.3% vs. 11%; p<0.04) and higher mean body mass index (28.4 kg/m² vs. 26.6 kg/m²; p=0.02) compared to the patients without. There was a statistically significant increase in 2 years all-cause mortality: 1.9% for reference category, 11.4% for patients who slept less than 6 hours, and 26.9% for patients who slept more than 8 hours per night; p value for trend =<0.0001.

Conclusions: Sleep disturbances were highly prevalent in STEMI patients. Physicians should routinely screen and evaluate myocardial infarction patients for sleep duration. Our findings suggest that short and long duration of sleep in first months after STEMI are associated with a greater risk of death.
were significantly predictive of future MACE. Only Mon 2 counts were an independent predictor of MACE after adjusting for age and sex (Table 1).

### Table 1. Predictive value of monocytes in MACE

<table>
<thead>
<tr>
<th>Monocytes</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenocty classification and enumeration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Monocytes (×10^9/l)</td>
<td>1.002 (1.000-1.004)</td>
<td>0.032</td>
</tr>
<tr>
<td>Mon1</td>
<td>1.001 (0.998-1.003)</td>
<td>0.111</td>
</tr>
<tr>
<td>Mon2</td>
<td>1.008 (1.003-1.013)</td>
<td>0.047</td>
</tr>
<tr>
<td>Mon3</td>
<td>1.01 (0.999-1.022)</td>
<td>0.388</td>
</tr>
</tbody>
</table>

### Conclusion:
Increased total monocyte and Mon 2 counts in the first 24 hours post infarction are predictive of MACE in STEMI patients. Mon 3, despite an assumed role in reparation and fibroblast deposition, was not predictive of MACE in post-STEMI patients. This suggests a specific role for Mon2 monocyte subset in post-infarction recovery in STEMI, and a potential role of this subset as a future therapeutic target. Remodelling data from cardiac magnetic resonance is awaited.

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**P5096 Prediction of late mortality after myocardial infarction by means of the GRACE Score in contemporary treated patients**

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**Background:** The GRACE Score (GS) was proposed for prediction of early and late mortality risk in acute coronary syndrome (ACS) patients. The GS includes age, history of congestive heart failure and previous myocardial infarction, these rate, systolic blood pressure and presence of ST-segment depression at admission, and serum creatinine, cardiac enzymes and percutaneous coronary intervention (PCI) during hospitalization. GRACE was developed and validated in patient with ACS collected in a multinational registry between 1999 and 2003. Less than one third of the registry patients were treated with PCI. Aim of this study was to investigate the predictive power of the GS in contemporary treated post-infarction patients.

**Methods:** 941 consecutive AMI patients aged <81 yrs were included. 93% underwent a PCI, 95% received beta-blockers, 94% ACE inhibitors and 95% statins. The GS was calculated according to the published protocol. Uni- and multivariable analyses were performed with traditional risk stratifiers like LVEF <35%, and diabetes mellitus. Follow-up was up to 5 years. Primary endpoint was total mortality. Follow-up was 5 years. Primary endpoint was total mortality.

**Results:** During follow-up, 72 patients (7.7%) died. The GS shows the strongest association with mortality in the univariate analyses followed by reduced LVEF and diabetes mellitus (see Table). By analyzing the different components of the GS in a multivariant analysis, only age, serum creatinine and history of previous myocardial infarction were independent and significantly associated with mortality (HR CI 1.09 (1.06 - 1.12); 1.82 (1.42 - 2.34); 2.01 (1.12 - 3.63)).

**Conclusion:** The GS is a strong risk predictor of 5-year mortality after acute myocardial infarction in a contemporary treated patient population and independent of reduced LVEF and diabetes mellitus. Age, serum creatinine and history of prior myocardial infarction carried the most predictive information of the GRACE score.

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**P5097 Impact of gender on clinical profile and long-term outcomes in patients with early-onset myocardial infarction**

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**Purpose:** Epidemiological and clinical data suggest that women with premature coronary artery disease have different risk factor profiles and angiographic characteristics from those of young men. Aim of this study was to assess gender-related differences in risk factors, clinical profiles, angiographic characteristics and long-term clinical outcomes in young patients with early-onset myocardial infarction.

**Methods:** This was a nationwide, prospective, observational cohort study of 2008 patients (1786 men and 223 women, mean age 39.60 years) hospitalized for STEMI between January 1988 and January 2002. Their baseline clinical and angiographic variables were recorded, and follow-up information regarding cardiovascular death, reoccurrence of myocardial infarction and coronary revascularization was obtained for a median of 9.4 years (interquartile range 8.1 to 12.1 years), a total of 19,385 person-years.

**Results:** Among traditional risk factors, smoking (87.42%) and a family history of coronary artery disease (81.52%) were the most prevalent, whereas hypertension and diabetes were less frequent (27.66% and 7.62%). Women had lower rates of smoking (73.54% vs 89.16%, p<0.0001), hypercholesterolemia (47.06% vs 63.33%, p<0.0001), diabetes mellitus (45.5% vs 47.59%, p<0.0001), hypercholesterolemia (47.06% vs 63.33%, p<0.0001) and obesity (11.93% vs 20.57%, p<0.0001), but were more likely to be physically inactive (63.23% vs 50.17%, p<0.0001). The most common coronary angiography finding in both groups was single- vessel disease (46.51% vs 47.59%, p=NS). Men were more likely to have two-vessel and multivessel disease (9.30% vs 22.60%, p<0.0001; 5.12% vs 14.35%, p<0.0001), whereas women were more likely to have normal coronary arteries and non-significant disease (25.11% vs 18.19%, p<0.0001; 10.70% vs 5.87%, p<0.0001). Women also had a higher incidence of spontaneous dissection and muscular bridges (5.58% vs 7.0%; p<0.0001; 2.33% vs 0.75%, p=0.041). During long-term follow-up, the mortality rate was low in both men and women (7.06% vs 6.01%, p=NS), but the results were not significantly different between men and women. One-year mortality rate was 51%: 64% in the PCI group and 24% in the CABG group. One-year mortality rate was 54% (69% PCI; 24% CABG, figure 1). Major adverse cardiac and cerebrovascular event (MACE) rates were 58% (30-day) and 84% (1-year). Diabetes mellitus (HR 2.9, 95% CI 1.3-6.3, p<0.009) and TIMI 0 flow (HR 3.1, 95% CI 1.2-8.3, p=0.017) were independent predictors for 30-day mortality. Angiographic characteristics were independent predictors for revascularization treatment: TIMI 0 flow strongly predicted performing PCI, and distal (bifurcated) LM lesion predicted performing CABG.

**Conclusions:** This is the first study to report ULMA related AMI data including in both PCI and CABG treated patients. Clinical results are worse in male patients, most likely due to selection bias. This is demonstrated by TIMI 0 flow and distal LM disease to be independent predictors for treatment choice.

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**P5098 Clinical outcomes after percutaneous or surgical coronary revascularization of unprotected left main coronary artery related myocardial infarction: a single-center experience**

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**Purpose:** Unprotected left main coronary artery (ULMA) related acute myocardial infarctions (AMI) are clinically catastrophic events. Due to the rarity of these events, only limited clinical data is available. Therefore, we evaluated 30-day and 1-year clinical outcomes after percutaneous or surgical coronary revascularization in these patients.

**Methods:** Between January 1998 and December 2008, 87 patients with ULMA related AMI have undergone revascularization treatment in our institution (57 with PCI, 30 with CABG). Clinical follow-up was obtained retrospectively by means of in- and outpatients medical charts. Patient’s vital status was verified with the national population registry. Cumulative event rates were estimated using the Kaplan–Meier method. Multivariate regression analyses were performed to identify predictors for 30-day mortality and PCI as revascularization treatment.
Probable effects of obstructive sleep apnea on plaque vulnerability and progression of coronary atherosclerosis in patients with acute myocardial infarction

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Aims: Impact of OSA on the clinical and angiographic follow-up outcomes in patients undergoing primary percutaneous coronary intervention (PPCI) has not been fully elucidated. We hypothesized that OSA may contribute to plaque vulnerability and cause adverse cardiovascular outcomes in patients who experienced acute myocardial infarction (AMI).

Methods: This study included a total of 272 patients with AMI who underwent PPCI. Polysomnography at first admission determined 124 patients with OSA defined as apnea-hypopnea index \( \geq 5 \) events/h. Clinical outcomes measured were cardiac death, recurrence of acute coronary syndrome (ACS), and re-admission for heart failure. Major adverse cardiac events (MACE) were defined as composite of end points of individual clinical outcomes. Follow-up angiography was performed in 222 patients. Intervention measures were target lesion revascularization (TLR) and newly necessitated PCI (new PCI) owing to disease progression.

Results: A mean follow-up duration was 4.0±1.7 years. Patients with OSA had more experienced the recurrence of ACS and MACE than control patients (17.6% vs. 6.6%, p=0.010; 21.8% vs. 10.3%, p=0.014). TLR was not different between the two groups (5.3% vs. 6.6%, p=0.010). Logistic regression analysis adjusted for different risk factors showed that the OSA was an independent predictor of recurrence of ACS and MACE (hazard ratio=1.98, p=0.027).

Conclusions: OSA may contribute to plaque vulnerability and cause adverse cardiovascular outcomes in patients who experienced acute myocardial infarction.

Chest pain patients with false positive hs-TnT in emergency department have the same one year risk of MACE as those who were hospitalized for acute coronary syndrome

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Background: The introduction in clinical practice of high sensitivity troponin (hs-Tn) assays has led to an increased diagnostic accuracy for Acute Coronary Syndrome (ACS) characterized by a higher sensitivity at the cost of a lower specificity leading to more false positive (FP) cases. The prognostic value of hs-Tn in false positive subjects has not been reported yet.

Methods: Four hundred and fifty-two (452) pts, admitted to ED because of chest pain, were enrolled. Serum levels of Roche hs-TnT were measured from baseline samples. All pts received a telephonic follow up (FU) contact at 30 and 360 days. The endpoint was the composite of MACE. Prognostic accuracy was evaluated by Kaplan-Meier curves.

Results: 60 pts were discharged with a diagnosis of ACS (13% of overall population) according to current guidelines. At follow up 412 patients were in good health, 8 had died (5 for cardiac causes and 3 of cancer) and 16 had experienced an episode of ACS (16 pts were lost to follow up). Among patients with negative hs-TnT at ED admission MACE were 3%, but were 8.5% in the group of FP and 12% in the true positive. Kaplan-Meier curves showed a significant difference in event-free survival between pts negative to hs-TnT versus FP pts (p=0.03) and versus true positive pts (p=0.004). However the last two group had a similar event free survival (p=0.5).

Prognostic impact of plasma aldosterone levels on long term outcome after myocardial infarction

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Background: It was reported higher aldosterone (ALD) levels were predictors of mortality risk in patients with heart failure or myocardial infarction (MI). The prognostic significance of ALD in the Japanese patients with acute myocardial infarction remains unknown.

Methods: Baseline plasma ALD levels were quantified in a prospective cohort study of 214 consecutive Japanese patients with acute MI (170 men, 44 women, age 67.8±12.6) to determine if there was an association of ALD levels and long term cardiac events. The subjects were divided into two groups of elevated ALD group (group H) and non-elevated ALD group (group L) according to the median value of baseline plasma ALD for data analysis. The primary end point of the study was cardiac death. The secondary end point was left ventricular ejection fraction (LVEF) at 6-month follow-up. For heart failure, all patients with OSA had a higher incidence of cardiac death, as compared to those of group L (N=107) with lower ALD (55.2% vs. 64.3%, P=0.0009). The LVEF at 6-month follow-up of group H was significantly lower than those of group L (55.2% vs. 64.3%, P=0.0001).

Conclusions: In pts admitted to ED for chest pain, a positive value beyond the hs-TnT cut-off (14 pg/ml) is associated with a similar prognostic value in true and false positive patients, suggesting that the latter group should receive an accurate work-out in ED and a careful follow-up after discharge.

Acute coronary syndromes in the elderly

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Background: Elderly patients (pts) with acute coronary syndromes (ACS) are frequently underrepresented in clinical trials which serve as source of evidence-based data used for practice guidelines. Aim: characterize and evaluate the compliance to guideline-oriented therapies and clinical outcomes in elderly patients with ACS in community practice.

Methods: Analyzed 30.161 patients with ACS consecutively included in a nationwide registry. We clustered pts into four age groups: <65, 65 to 74, 75 to 84, and ≥85 years old. In our analysis, young pts refer to those <65 years of age. We compared pts’ baseline demographics, clinical characteristics, care patterns, and in-hospital outcomes. Early medication compliance score was created, attributing one point for each of the following: aspirin and clopidogrel (1 point), any heparin (1 point), beta-blockers (1 point), angiotensin-converting enzyme (ACE) inhibitors (1 point), lipid-lowering agents (1 point). Discharge medication compliance score was also created, attributing one point for each of the following: aspirin and clopidogrel (1 point), beta-blockers (1 point), ACE inhibitors (1 point), lipid-lowering agents (1 point). In-hospital clinical outcomes of interest included all cause in-hospital mortality, major adverse cardiac events (MACE) (as defined in in-hospital death, re-infarction and stroke).

Results: Fifty seven percent of the population was 65 years or older. During their hospitalization, elderly pts were less likely to use guidelines-recommended therapies as evaluated by the compliance score analysis. Elevation scores to undergo coronary angiography or revascularization procedures. With advancing age, elderly pts had a higher incidence of in-hospital events (Table 1).

Conclusion: Age has a negative impact on the use of guidelines-recommended
Baseline hypercalcaemia in acute coronary syndrome patients: a five-year outcome study


Background: Serum calcium level has been associated with ischaemic myocardial infarction (MI), but its role as a predictor of outcome in patients with acute coronary syndromes (ACS) was not determined. The aim of this study was to assess the role of admission calciumaemia in predicting adverse outcomes, among ACS patients.

Methods: Serum calcium was measured at admission in 365 patients with ACS. Data on sociodemographic and clinical characteristics were evaluated. The occurrence of a composite outcome (all-cause mortality and hospitalization for congestive heart failure [CHF] or ACS) was assessed at 60 month follow-up.

Results: Among all, 71% patients were male and the mean age was 64±13 years. Mean serum calcium was 2.36±0.33 mmol/L and 20% of patients had hypercalcaemia (≥ 2.60 mmol/L). Patients with hypercalcaemia were more frequently women (45% vs 25%; p=0.001), diabetic (43% vs 24%; p=0.001), hyper-tensive (74% vs 60%; p=0.017) and presented more kidney disease (KD) (49% vs 21%; p<0.001) as well as left ventricular (LV) systolic dysfunction (45% vs 28%; p=0.010).

At 5 year follow-up, composite outcome occurred in 92 (25%) patients and occurred more frequently in patients with hypercalcaemia (41% vs 22%; p=0.001). Furthermore, this patient group presented a significant preponderance of adverse events: ACS (25% vs 12%; p=0.001), CHF requiring hospitalization (16% vs 5%; p=0.003) and death (25% vs 10%; p=0.001), LV dysfunction (44% vs 27%; p=0.003), diabetes (37% vs 25%; p=0.020), hypertension (72% vs 60%; p=0.021) and KD (40% vs 22%; p=0.001) were also associated with the occurrence of composite outcome.

Kaplan-Meier analyses indicated that hypercalcaemia was a predictor of the composite adverse outcome (HR 2.2; CI 1.4-3.4). Multivariate survival analysis using Cox’s regression model, including hypercalcaemia, LV systolic function and KD confirmed the independent association of hypercalcaemia with adverse outcome (HR 1.7; CI 1.1-2.8).

Conclusions: Hypercalcaemia is an independent predictor of long-term adverse outcomes. High serum calcium concentration may constitute a cost-effective and important prognostic indicator for ACS patients.

Serum uric acid: a forgotten prognostic marker in acute coronary syndromes?

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Background: Serum uric acid (UA) has been shown as an independent risk factor for coronary artery disease. There are however limited data regarding the prognostic value of UA in the context of acute coronary syndromes (ACS).

Methods: Study of consecutive patients admitted with an ACS (with and without ST-segment elevation) at a single-centre coronary care unit. Primary end-point was all-cause mortality at one-year follow-up. Independent predictors of UA were obtained by linear regression analysis. ROC curve analysis was performed to obtain the best cut-off of UA to predict mortality and the groups obtained by that cut-off were compared by Kaplan-Meier analysis. Logistic regression analysis was also performed to adjust the predictive value of UA as a categorical variable, as well as a continuous variable.

Results: We included 683 patients, mean age 64±13 years, 69% males. In-hospital and one-year mortality were 4.2% and 7.2% respectively. The best cut-off for UA to predict one-year mortality was 6.25 mg/dL (sensitivity 59%, specificity 72%) and 30.2% had an increased UA according to this cut-off. Independent predictors of UA were male gender (β=0.078), body mass index (β=0.163), diuretics before admission (β=0.142) and admission serum creatinine (β=0.403). One-year mortality was significantly higher in patients with increased UA (14.1% vs. 4.2%, OR 3.74, 95% CI 2.06 – 6.79, p<0.001) and the same was observed by survival analysis (Log rank, p<0.001). After adjustment, both increased UA as a categorical variable (OR 2.06, 95% CI 1.01 – 4.20, p=0.046) and as a continuous variable (OR 1.29, 95% CI 1.11 – 1.51, p<0.001) are independent predictors of mortality. In patients with high risk GRACE score, increased UA improves predictive accuracy of mortality (21.7% vs. 8.4%, p<0.002). However, in the other GRACE risk score classes, UA couldn’t discriminate mortality.

Conclusions: Serum UA is an independent predictor of all-cause mortality in the medium-term after ACS and can improve prediction in the high risk GRACE score group.

Prognostic role of flow mediated dilation in patients with no-ST-segment elevation acute coronary syndrome

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Purpose: Endothelial dysfunction (ED) has been shown to predict cardiovascular outcome in several clinical settings. In this study we assessed severity, time course and clinical implications of ED in patients with no-ST-segment elevation acute coronary syndrome (NSTE-ACS).

Methods: We studied 60 patients (62±8 years, 44 M) with NSTE-ACS and 40 patients (63±10 years, 27 M) with stable coronary artery disease (CAD). Endothelial function was assessed within 72 hours of admission by measuring dilation of the brachial artery after 5 minutes of forearm ischaemia (flow-mediated dilation, FMD). FMD was reassessed 3 months after the acute event. The combined end-point included cardiac death, new ACS and hospitalization for recurrence of angina.

Results: On admission, FMD was lower in NSTE-ACS than in stable CAD patients (2.1±1.2% vs. 4.7±2.1%; p<0.001). FMD improved significantly at 3-month FU in NSTE-ACS patients (to 5.7±2.6%; p<0.01). During a median follow-up of 32 months (range, 14-36), 14 (32%) cardiac events occurred in NSTE-ACS patients. A very low FMD (<4%) was associated with a lower event-free survival in NSTE-ACS patients (Figure). At multivariable logistic regression, including age, gender, cardiovascular risk factors and C-reactive protein levels, only diabetes (HR 7.29, 95% CI 2.69-19.6) and FMD on admission (HR 0.62, 95% CI 0.44-0.89) and at 3 months (HR 0.79, 95% CI 0.66-0.94) were independent predictors of the combined cardiac end-point in NSTE-ACS patients.

Predictive value of advanced glycation end products for the development of post-infarction heart failure


Introduction and objectives: Taking into account that the post-infarction heart failure (HF) determines a great morbimortality, together with the physiopathological implications of advanced glycation end products (AGE) in the genesis of myocardial dysfunction, it was intended to analyze the prognostic value of these molecules to predict the development of HF after a coronary event.

Methods: AGE were measured by fluorescence in 194 patients consecutively admitted to the coronary unit due to a myocardial infarction. It was analyzed the
association between glycemic parameters and the development of post-infarction HF. Finally, we identified the variables with a independent predictor value by a multivariate analysis of Hazard ratio by Cox regression.

**Results:** Of 194 included patients, 11 (5.6%) developed HF during follow-up (median: 1.0 years [0.8 to 1.5 years]). Glucose, fructoseamine, glycated haemoglobin and AGE were predictors of post-infarction HF in the univariate analysis. After adjustment for confounding variables only AGE (Hazard Ratio 1.016, IC 95%: 1.006-1.026; $p$ < 0.001), together with NT-proBNP and the infarction extension (measured by the troponin I peak), were predictors of the development of post-infarction HF. AGE levels over the median multiplied by 5 the risk of developing HF during the follow-up.

**Conclusions:** High levels of advanced glycation end products (AGE) are an independent predictor for the development of post-infarction HF.

### P5108

**Risk stratification by kllp class and left ventricular systolic function in patients with acute myocardial infarction in modern era from Korean acute myocardial infarction registry**

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**Purpose:** The aims of this study were to determine the interactive effect of Killip class and left ventricular systolic function on 12-month mortality in patients with acute myocardial infarction (AMI) in modern era.

**Methods:** Between November 2005 and January 2008, 8,418 eligible patients (5,842 mm, mean age = 67±12.5 years-old) were analyzed from the Korean AMI Registry. Patients were stratified into 4 groups based on Killip class (1 versus ≥2) and left ventricular ejection fraction (LVEF; <50% versus ≥50%); group 1 (Killip class 1 and LVEF ≥50%, n=4,003), group 2 (Killip class 1 and LVEF <50%, n=851), and group 4 (Killip class ≥2 and LVEF <50%, n=1,344). The LVEF were measured by two-D echocardiography.

**Results:** The 12-month mortality was 2.0% in group 1, 7.3% in group 2, 10.6% in group 3, and 22.5% in group 4, respectively. Kaplan-Meier survival showed there was significant difference in 12-month mortality among 4 groups (log-rank $p$ < 0.001). Patients in group 2 had significantly higher 12-month mortality compared with patients in group 1 (Hazard ratio [HR] 3.952, 95% confidence interval [CI] 2.728 to 5.610, $p$ < 0.001), as did patients in group 3 (HR 3.991, 95% CI 2.592 to 6.152, $p$ < 0.001) after adjustment for clinical variables and angiographic variables in Cox proportional hazards model. In fully adjusted model including also medications during hospitalization and discharge, patients in group 2 had significantly higher 12-month mortality compared with patients in group 1 (HR 4.034, 95% CI 2.786 to 5.921, $p$ < 0.001), as did patients in group 3 (HR 3.395, 95% CI 2.125 to 5.310, $p$ < 0.001). The patients in group 4 had the highest 12-month mortality compared to patients in group 1 after adjustment for clinical and angiographic variables (HR 8.922, 95% CI 5.821 to 11.784, $p$ < 0.001), and after adjustment for clinical, angiographic, and discharge medications (HR 7.748, 95% CI 5.372 to 11.176, $p$ < 0.001).

**Conclusions:** Despite technical improvement and new medical treatment in modern era, the conventional risk stratification by Killip class and LVEF still provide prognostic implication on 12-month mortality in post-MI patients.

### P5109

**Early effects of ivabradine in combination with beta-blockers compared to beta-blockers on systolic and diastolic function in STEMI and NSTEMI patients**

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**Purpose:** To compare the early impact of heart rate (HR) control with ivabradine plus metoprolol and metoprolol uptitration on left ventricular (LV) systolic and diastolic function, serum NT-proANP and exercise capacity in anterior Q-MI pts with EF<45%.

**Methods:** In single-blind parallel-group study 62 pts with a first Q-MI, EF 30-45%, sinus rhythm > 80 bpm, Killip class I-II were randomized 1:1 to ivabradine plus beta-blockers (BB) and BB uptitration groups Pts with anterior MI (24 and 18 respectively) were included in this analysis. Pts in Group 1 from day (D) 0 to D 25 were uptitrated to 4.6-50mg bid (66.1±1.9 mg pd on top of which from D 4-6 ivabradine 2.5 mg bid was uptitrated to 7.5 mg bid. Pts in Group 2 were uptitrated to 75 mg metoprolol bid (117.6±4.9 mg pd). Besides, EF was a systolic inflow DT at D 1 and 21 early mitral inravals velocity (E') was filling velocity (E) by TDI at D 5 and 25, serum NT-proANP at D 2 and 25 were estimated. Symptom-limited treadmill test (Bruce protocol) was performed at D 21 and 25.

**Results:** Resting HR was similar in both groups at D 1 (86.7±17.1 vs. 87.5±16.1 bpm), D 5 (68.4±15.5 vs. 68.1±1.4 bpm) and D 25 (60.7±17.7 vs. 61.6±8.5 bpm, $p$ > 0.05). Echo-Doppler and NT-proANP data (M±m) see in the Table. Group 1 compared to Group 2 higher exercise capacity (4.9±3.7 vs 4.0±2.0 MET) and duration (20±6.1±2.3 vs 16±12.3±0.8, $p$ < 0.05) were attained in spite of higher HR at peak load (105±2.5±1 vs 99±2.3±0.9, $p$ < 0.01).

**Conclusions:** In pts after anterior MI with LV EF<45 of systolic dysfunction, addition of ivabradine to metoprolol, in comparison with up titration of metoprolol was associated with decrease of serum NT-proANP level, improvement of systolic and diastolic function and exercise capacity in spite of larger increase of HR at peak workload by D 25.
end of observation; cut-point of 105 points displayed 58.5% sensitivity and 70.7% specificity). Multivariate analysis identified additional independent risk factors for long-term mortality (Table).  

Conclusions: There are some risk factors obtained both from the medical history and during the hospitalization that could increase the power of the risk stratification model. This suggests need for particular risk stratification performed in discharge in context of long-term period.

P5111  Prognosis importance of absence of angina in non-ST elevation myocardial infarction  

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Purpose: Cardiac troponins increased myocardial infarction diagnosis in patients without specific electrocardiographic changes. Absence of angina has become common and prognostic significance remains unclear.

Methods: We followed 204 consecutive patients after myocardial infarction non-ST elevation (NSTEMI) at emergency department. Outcomes were in-hospital death and follow-up death or cardiac readmission.

Results: No-angina (NAG) group (n = 27, 13.2%) had more women (p = 0.001), higher blood glucose (p = 0.011) and B-type natriuretic factor (p < 0.001). In-hospital (14.8% vs 4.5%; p = 0.035) and 20-months follow-up mortality (43.5% vs 12.9%, p = 0.001) were higher in NAG. Combination of death and cardiac readmissions was similar (70.4% vs 53.1%; p = 0.093). Age (HR = 1.038, 95% CI 1.006 to 1.071), absence of angina at admission (HR 2.554, 95% CI 1.037 to 6.289), male gender (HR 2.706, 95% CI 1.099 to 6.667) and dyspnea (HR 3.113, 95% CI 1.417 to 6.842) were independent predictors of long-term mortality.

Figure 1. Kaplan-Meier curve

Conclusion: The absence of chest pain in NSTEMI implies in higher in-hospital and long-term mortality.

P5112  Is female gender a real independent predictor of mortality after acute coronary syndrome?  

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Background: Female gender has been described as an important predictor of outcome after elective coronary interventions. Is this ominous influence of female gender also present in the context of acute coronary syndromes (ACS)? Methods: Study of consecutive patients admitted for an ACS at a single-centre coronary care unit. Kaplan-Meier analysis and Cox regression analysis regarding the primary end-point of all-cause mortality at 30 day and one-year follow-up were performed to investigate the influence of gender on outcome.

Results: The study included 1423 patients, with a mean age of 64±13 years, 31% females. Thirty-day and one-year mortality were 6.7% and 8.5% respectively. ST-segment elevation acute myocardial infarction (STEMI) was present in 60.2% of the patients. Females were more elderly (70±12 vs 61±12 years, p<0.001), had more hypertension and diabetes and were less smokers. Heart rate and GRACE risk score were higher in females and estimated glomerular filtration rate lower. Females presented more often in Killip class ≥ 2, but had similar left ventricular ejection fraction. STEMI was more frequent in males (64.6% vs. 50.6%, p<0.001). Kaplan-Meier analysis in the entire population, showed a significant increase in the incidence of the primary endpoint in females in comparison to males (Logrank, p=0.030, HR 1.49, 95% CI 1.04 – 2.05). However, analysing different age strata, females had identical mortality compared to males of the same age group (Table 1). On the other hand, 69% of women had an age ≥ 65 years, suggesting an important effect of age. After adjustment for age, female gender was no longer a predictor of mortality (HR 0.85, 95% CI 0.58 – 1.24, p=0.404).

Conclusions: Female gender is not a predictor of all-cause mortality after ACS. In fact, age is a major confounder in the influence of gender on outcome and must be taken into account, since women admitted with an ACS are significantly older than men.

Table 1. All-cause mortality by age strata

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Overall</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ≥ 60</td>
<td>682</td>
<td>444</td>
<td>238</td>
<td>136</td>
<td>80</td>
</tr>
<tr>
<td>60 ≤ 74</td>
<td>470</td>
<td>363</td>
<td>107</td>
<td>166</td>
<td>29</td>
</tr>
<tr>
<td>&gt; 74</td>
<td>182</td>
<td>126</td>
<td>56</td>
<td>80</td>
<td>27</td>
</tr>
</tbody>
</table>

P5113  Peak Systolic Velocity (PSV) using colour-coded Tissue Doppler Imaging (TDI) is a strong and independent predictor of outcome in acute coronary syndrome patients  

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Background: Traditional echocardiographic methods like left ventricular ejection fraction (EF) and wall motion scoring (WMS) and new methods like speckle tracking (ST) based 2D strain and strain rate carry important prognostic information in acute coronary syndrome (ACS) patients. Parameters from tissue Doppler imaging (TDI), with its high time resolution, may further increase the prognostic value. Peak systolic velocity (PSV) of the basal segments of the left ventricle from TDI is a robust and user independent parameter. The aim was to investigate the prognostic value of PSV compared to EF, WMS, 2D strain and strain rate.

Methods: Echocardiographic images were collected and post processed in 227 ACS patients. Additional clinical data was prospectively gathered and patients were followed for 3-5 years regarding the combined endpoint of death or re-admission due to ACS or heart failure.

Results: The combined endpoint occurred in 84 (37%) patients. Those with an event had lower median PSV than those without (4.4cm/s vs. 5.3cm/s), (p<0.001). In a ROC analysis, the AUC was larger for PSV (0.74) than for EF (0.68), WMS (0.65), 2D strain (0.71) and strain rate (0.69). The combined endpoint increased with decreasing PSV (figure). When adjusting for differences in baseline characteristics in a COX-regression model, PSV remained independently associated with outcome where the others did not. PSV was also less sensitive to image quality with fewer values missing or unacceptable for analysis.

Conclusions: Peak systolic velocity (PSV) using colour-coded TDI is a robust measurement that seems to have a stronger association with outcome than traditional measurements such as EF and WMS, and more recently established measurements such as 2D strain and strain rate, in ACS patients.

P5114  Left atrial volume and dynamics in chronic kidney disease  

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Background: Left ventricular changes in end stage renal failure are well recognised; however, little is known about the same in early stages of chronic kidney disease. Cardiac troponin (CKD) and associated changes in cardiac function included left ventricle mass and left atrial volume. We aimed to determine an early stage of CKD and associated changes in cardiac function.

Methods: 50 CKD patients (eGFR 30-60 ml/min/1.73m2), underwent a transthoracic echocardiogram and were compared with 49 normal subjects as well as 30 hypertensive subjects. LV ejection fraction and LV mass indexed to body surface area (LUMI) were measured. Biplan LA volume indexed to body surface area (LAVI), LA global and segmental function was measured using 2-dimensional strain imaging in the apical four and two chamber views from the septal and lateral walls using 2D speckle tracking. Systolic (S-G), early (E-G) and late (A-
Next generation sequencing approach for the diagnosis of heart disease patients using a panel of 72 genes

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Purpose: Genetic characterization of heart disease patients in a fast, comprehensive, and cost-effective manner using a 72 gene NGS approach, coupled with a custom bioinformatics pipeline.

Methods: We developed a methodology for resequencing 72 genes (44 genes associated with cardiomyopathy, arrhythmogenic right ventricular dysplasia, Marfan syndrome, aortic aneurysm, and 28 genes associated with Brugada syndrome, long QT syndrome, and abnormal 6MWT for the AF development was 10.9 (95%CI 3.1-37.7), which was greater than that of ALP (2.8, 95%CI 1.2-6.7) or 6MW (3.2, 95%CI 1.3-7.5).

Conclusion: The combination of ALP and 6MW would improve the prediction of the AF development in CHF patients.

Abstract P5116 – Figure 1. Atrial dyssynchrony

Abstract P5116 – Table 1. Patient characteristics, atrial conduction times and atrial dyssynchrony

<table>
<thead>
<tr>
<th></th>
<th>Control (n=35)</th>
<th>Narrow GRS (n=35)</th>
<th>Wide GRS (n=35)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean±SD</td>
<td>mean±SD</td>
<td>mean±SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>59.3±10</td>
<td>58.5±11</td>
<td>59.1±10</td>
<td>0.70</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>27 (77.1)</td>
<td>26 (74.3)</td>
<td>28 (80)</td>
<td>0.604</td>
</tr>
<tr>
<td>LV Ejection Fraction (%)</td>
<td>64±5.3</td>
<td>65±4.4</td>
<td>65±4.3</td>
<td>0.012</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>22 (62.9)</td>
<td>22 (62.9)</td>
<td>22 (62.9)</td>
<td>0.76</td>
</tr>
<tr>
<td>Non ischemic heart disease, n (%)</td>
<td>13 (37.1)</td>
<td>14 (43.7)</td>
<td>14 (43.7)</td>
<td>0.748</td>
</tr>
<tr>
<td>LA dyssynchrony (ms)</td>
<td>14.1±3</td>
<td>17.2±3</td>
<td>21.6±3</td>
<td>-0.01</td>
</tr>
<tr>
<td>RA dyssynchrony (ms)</td>
<td>14.6±4</td>
<td>22.8±4</td>
<td>37.1±7</td>
<td>-0.001</td>
</tr>
<tr>
<td>Intersatial dyssynchrony (ms)</td>
<td>29.1±4</td>
<td>40.2±5</td>
<td>54.7±7</td>
<td>-0.001</td>
</tr>
</tbody>
</table>

*p<0.05 compared to normal; **p<0.05 compared to HT group.

Conclusion: LV diastolic dysfunction starts in early stages of CKD with consequent atrial changes as demonstrated by LA enlargement and reduced global as well as phasic functions. The severity of LA changes in CKD appears to exceed that due to the presence of LV hypertrophy as LAI was significantly greater and LA function parameters significantly lower even compared to a cohort with hypertension with preserved kidney function.
Nicorandil improved electrical and structural remodeling and prevented ventricular tachyarrhythmias in a mouse model of desmin-related cardiomyopathy.

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Introduction: It is well known that cardiac arrhythmias were observed in patients with desmin-related cardiomyopathy. Transgenic (HSBP5 R120G-TG) mice with overexpression of an arg120gly (R120G) missense mutation in HSBP5 display desmin-related cardiomyopathy. Recently, cardioprotective effect of nicorandil, a K+ ATP-sensitive potassium channel opener and NO donor, prolongs survival in HSBP5 R120G-TG mice. However, whether the TG mice induce ventricular arrhythmias and nicorandil can inhibit the arrhythmias remains unknown. Therefore, we examined the effects of chronic administration of nicorandil on ventricular electrical and structural remodeling and arrhythmias in HSBP5 R120G-TG mice.

Method and Results: Nicorandil (15mg/kg/day) or vehicle was orally administered in HSBP5 R120G-TG mice from 5 weeks to 30 weeks of age. Ventricular function was investigated at the age of 30 weeks using two-dimensionally-directed M-mode echocardiography. Electrocardiogram (ECG) lead II and optical action potentials were recorded from HSBP5 R120G-TG mice and the epicardial surface of the Langendorff-perfused TG mouse hearts, respectively at the age of 30 weeks. We also examined the expression of ventricular gap junction proteins (connexin43) in the TG mice using western blots. Nicorandil improved ventricular dysfunction, determined by reduction of LV fractional shortening in HSBP5 R120G-TG mice. Nicorandil also improved the prolonged P, PQ, and QT intervals at the ventricle induced tachyarrhythmias (VT) in 6 of 8 vehicle-treated HSBP5 R120G-TG mice but in none of 8 nicorandil-treated HSBP5 R120G-TG mouse hearts (p < 0.05).

Conclusion: These findings suggest that nicorandil can inhibit ventricular electrical and structural remodeling and prevent VT induction in a mouse model of desmin-related cardiomyopathy.

Left ventricular diastolic and systolic and atrial dysfunction in patients with hypertension might be related to increased oxidative stress and inflammation-final results

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Purpose: To study the presence of oxidative stress, inflammation, hypercoagulability and neuroendocrine activation in patients with hypertension (HT).

Methods: Results from >60-year-old 112 patients (18 controls and 94 patients with HT) (HT) or normal ejection fraction (EF) are presented. All subjects had echocardiography with assessment of atrial and left ventricular (LV) systolic and diastolic function. Determination of (1) oxidative stress [measurement of total scavenger capacity (TSC), protein carbonylation (PK), tetrazolium reductase (B/H4) levels], (2) inflammatory [measurement of C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-a (TNF-a)] levels), (3) coagulation [measurement of fibrinogen levels, plasminogen activator inhibitor (PAI-1) and von Willebrand factor], and (4) neuroendocrine parameters [cholesterolin A (cGA) and B-type natriuretic peptide (BNP)] levels was carried out from plasma or serum samples.

Results: 36/94 (40%) patients with HT had no diastolic dysfunction (HTDD- group) and 56/94 (60%) patients had diastolic dysfunction (HTDD+ group). TSC decreased and BHF increased in both patient groups (p < 0.01 for both groups respectively), PK increased (p < 0.05) in the HTDD- group. CRP increased (p < 0.05) in the HTDD+ group and IL-6, TNF-a, PAI-1, cGA, BNP increased (p < 0.001 and p < 0.05) in both groups; p < 0.05 and p < 0.01 respectively in both patient groups compared with controls. No between groups difference was found in other laboratory parameters. The absolute values of the mean of maximal longitudinal systolic LV strain (S) (p < 0.05 for both groups) and systolic (p < 0.01 for both groups) and early diastolic (p < 0.05 for both groups) and atrial reservoir period (p < 0.05 for both groups) were significantly reduced with controls. Numerous significant correlations between clinical and echocardiographic parameters were found. Typically the degree of oxidative stress and inflammation, BNP and PAI-I levels correlated inversely with LV systolic and diastolic and atrial function.

Conclusion: Increased oxidative stress and neuroendocrine activation might play a role in LV systolic and diastolic and atrial dysfunction.
Olmesartan inhibits ventricular remodeling and anti-arrhythmias in a mouse model of chronic heart failure

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Introduction: While beneficial effects of olmesartan, an angiotensin type 1 receptor blocker, on chronic heart failure (CHF) have been demonstrated, whether it has inhibitory effects on ventricular arrhythmias induced by CHF is still unclear. Recently, we demonstrated that a transgenic mouse with transient cardiac expression of activated G protein αq (Gq-TG) develops CHF and frequent ventricular arrhythmias. We examined the effects of chronic administration of olmesartan on ventricular function, the number of premature ventricular contractions (PVC), and ventricular remodeling in Gq-TG mice.

Methods and Results: A lower dose of olmesartan (LDO, 1mg/kg/day), higher dose of olmesartan (HDO, 3 mg/kg/day) or vehicle was orallyadministered to 30 Gq-TG mice from 6 weeks to 32 weeks of age. At the age of 32 weeks, systolic blood pressure (SBP) and electrocardiogram (ECG) were measured and ventricular function was also investigated using echocardiography. The degree of fibrillation was elucidated from left ventricular sections stained with Masson’s trichrome. Mean SBP was significantly decreased in HDO-treated Gq-TG mice compared with those in LDO and vehicle-treated Gq-TG mice (45±5.3 vs. 77±1.4 and 72±4.8 mmHg p<0.001). Both LDO and HDO-treated mice showed improved ventricular dysfunction, determined by reduction of LV fractional shortening (p<0.01) in Gq-TG mice. During 10 min of ECG recording, PVC was frequently (more than 20 beats/min) observed in 9 of 10 vehicle-treated Gq-TG mice but in none of 10 LDO-treated Gq-TG mice (p<0.01 by Fisher’s exact test). Interestingly, the number of PVC was not decreased in HDO-treated Gq-TG mice. Collected QT interval was significantly shorter in LDO-treated Gq-TG mice than in HDO and vehicle-treated Gq-TG mice (p<0.05). The degree of extensive interstitial fibrosis in the left ventricle was significantly less in both LDO and HDO-treated Gq-TG mice than in vehicle-treated Gq-TG mice (p<0.05).

Conclusions: These findings demonstrated that lower but not higher doses of olmesartan inhibited ventricular electrical remodeling and decreased the number of PVC in a mouse model of CHF, suggesting that relatively low dose of olmesartan is enough to treat CHF-induced ventricular arrhythmias.

Pitavastatin ameliorates experimental autoimmune myocarditis by decreased Th1/Th17 cytokines in mice

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Purpose: Experimental autoimmune myocarditis (EAM) in mice is a T cell-mediated disease and the involvement of Th1 and Th17 cytokines has been demonstrated. Statins, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, have anti-inflammatory and immune-regulating properties. This study was designed to test the hypothesis that pitavastatin affects T cell-mediated autoimmunity through inhibiting the production of Th1 and Th17 cytokines and reduces the severity of EAM.

Methods: BALB/c mice were immunized with murine cardiac myosin peptide emulsified in complete Freund’s adjuvant. Pitavastatin or vehicle was administered orally for 3 weeks to mice with EAM.

Results: Pitavastatin treatment reduced the pathophysiological severity of myocarditis and decreased heart-to-body weight ratio. We found that pitavastatin treatment inhibited the phosphorylation of signal transducer and activator of transcription 3 (STAT3) and STAT4 in the heart, and suppressed production of Th1 and Th17-type cytokines (interleukin [IL]-1β, IL-6, IL-17) by CD4+ T cells. Pitavastatin inhibited the differentiation of Th0 cells into Th1 and Th17 in vitro experiments. Plasma lipid levels did not differ between the groups.

Conclusions: Pitavastatin ameliorated EAM by inhibiting T cell responses and suppressing Th1 and Th17-type cytokine production. Statins may be beneficial for myocarditis and other Th1- and Th17-mediated diseases.
The mitochondrial translocator protein ligands, 4',chlorodiazepam and TRO40303 protect cardiomyocytes against doxorubicin toxicity

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Purpose: Doxorubicin is widely used as a chemotherapeutic agent for the treatement of a large spectrum of human neoplastic diseases but its administration in humans is limited by severe cardiotoxicity. Reactive oxygen species (ROS) production and mitochondrial permeability transition pore opening (mPTP) have been identified as major events in doxorubicin-induced damage. As the mitochondrial Translocator Protein (TSPO) ligands 4',chlorodiazepam (CDZ) and TRO40303 have been shown to protect mitochondria and to reduce left ventricular dysfunction during myocardial ischemia-reperfusion through the inhibition of the opening of the mPTP, we examined their potential protective effect on doxorubicin-induced loss of contractility and ultimately on cell death in isolated adult rat cardiomyocytes.

Methods: The effects of doxorubicin (0.25-20 μM) on contractile function were evaluated in isolated adult rat cardiomyocytes paced at 1Hz by electric field stimulation. Cell viability and ROS were determined with the fluorescent probes profluorescein isothiocyanate and dichlorofluorescein, respectively. Direct mPTP opening was assessed by the intracellular calcium loading CoCl2 staining method and confirmed by the preventive effect of cyclosporin A. CDZ and TRO40303 improved cell viability, prevented the alterations of contractility and attenuation of the collapse of maximal velocities of contractile and relaxation induced by doxorubicin. The cytoprotective effect of TSPO ligands involved a high reduction of doxorubicin-induced ROS production associated with inhibition of mPTP opening as attested by the maintenance of the mitochondrial calcium fluorescence observed in the presence of CDZ or TRO40303.

Results: At higher concentrations than 5 μM doxorubicin significantly reduced the velocities of contraction and relaxation of the cardiomyocytes and caused cell death. The deleterious effects of doxorubicin were associated with an increase in ROS production and involved mPTP opening as demonstrated using the calcine CoCl2 staining method and confirmed by the preventive effect of cyclosporin A. CDZ and TRO40303 improved cell viability, prevented the alterations of contractility and attenuated the collapse of maximal velocities of contraction and relaxation induced by doxorubicin. The cytoprotective effect of TSPO ligands involved a high reduction of doxorubicin-induced ROS production associated with inhibition of mPTP opening as attested by the maintenance of the mitochondrial calcium fluorescence observed in the presence of CDZ or TRO40303.

Conclusion: These data demonstrate that the TSPO ligands, CDZ and TRO40303 protect cardiac cells against doxorubicin toxicity and that this protection is at least in part mediated by prevention of ROS production and mPTP opening. Thus TSPO may represent a relevant pharmacological target for protection of the heart against doxorubicin-induced toxicity.

Adrenomedullin, ghrelin and leptin as potential biomarkers of chronic heart failure: an experimental study

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Introduction: Pathophysiology and biomarkers of heart failure are under extensive research. Recently, several regulatory peptides - primarily of non-cardiac origin - including adrenomedullin (ADM), ghrelin (GHR) and leptin (LPT) were identified as potential biomarkers of heart failure.

Objectives: We aimed to investigate plasma concentrations of the above peptides during development of experimental heart failure in comparison with the use of biomarkers pro-atrial natriuretic peptide (proANP) and endothelin-1 (ET-1).

Methods: Packer model was implanted in dogs (n=13) for rapid right ventricular pacing (240/min). Echocardiographic measurements, functional staging and blood sample collection for ADM, GHR, LPT, proANP and ET-1 measurements (ELISA) were performed weekly. Nonparametrical tests were used for statistical analysis.

Results: NYHA IV stage heart failure developed after 22±4 days of pacing. Echocardiography revealed seriously impaired left ventricular ejection fraction (means:SEM; EF: 22±3% vs 62±3% p<0.01), dilation of left (LVEDD: 37±2 vs 57±2 mm p<0.01) and right (LVEDD: 26±2 vs 20±1 mm p<0.01) ventricle, and increasing mitral and tricuspid regurgitation. Plasma levels of the examined peptides significantly increased during the development of heart failure (ADM: 440±53 vs 293±24 pg/ml p<0.01; GHR: 165±286 vs 95±139 pg/ml p<0.01; LPT: 750±241 vs 434±177 pg/ml; ET-1: 14±3.2 vs 9.2±1.4 pg/ml p<0.05; proANP: 628±11067 vs 801±167 pg/ml p<0.01). Significant positive correlation was found between left ventricular end-diastolic diameter and GHR, ET-1 and proANP levels (GHR: p=0.41, p<0.02; ET-1: p=0.57, p<0.01; proANP: p=0.40, p<0.01). The strongest correlation of biomarkers was found between proANP and GHR (r=0.37, p<0.05).

Conclusion: Right ventricular tachypacing induced chronic heart failure is suitable for examination of biomarker agents. Significant elevation of plasma adrenomedullin, ghrelin and leptin concentrations during the development of heart failure suggests the possible use of these peptides as novel biomarkers of the disease.

Study of vav3 ser298thr polymorphism in patients with heart failure


Background: Vascular endothelial growth factor (VEGF) plays a key role in angiogenesis and is required for preventing the transition from compensatory left ventricular hypertrophy (LVH) to heart failure (HF). Soluble VEGF receptor-2 (sVEGF-R-2), which retains an affinity for VEGF but is unable to activate its signal transduction, acts as an endogenous inhibitor of VEGF. Recently, we demonstrated that serum sVEGF-R-2 levels are increased in subjects with metabolic syndrome. However, the possible role of sVEGF-R-2 in LVH or HF in human is unknown.

Methods and Results: We recruited 434 consecutive outpatients with or without HF, whose NIHYA classes were stable for at least 3 months. Among them, 19 had LVH (LV mass index (LVM); male -116±16, female -104±24 g/m2) and systolic dysfunction (LV ejection fraction (LVEF) -<50% (LVM+HF)). From leaving 415 patients we selected age-, gender-, and the body mass index-adjusted 19 who had LVH and preserved systolic function (LVH+HF), and 19 who did not have LVH but had preserved systolic function (LVH+HF). Then, we measured serum levels of sVEGF-R-2 receptor-1 (sVEGF-R-1), and sVEGF-R-2 expressing enzyme-linked immunosorbent assays in 57 patients. Systolic and diastolic blood pressures, VEGF, and sVEGF-R-1 were similar among the 3 groups. NT-proBNP levels were higher in LVH+HF than LVH+HF and LVH+HF. In contrast, sVEGF-R-2 was significantly lower in LVH+HF than LVH+HF (P<0.02). After adjustment for age and gender, sVEGF-R-2 levels were positively correlated with triglycerides, LVEF, and negatively correlated with LVM and NT-proBNP. Stepwise regression analysis revealed that independent determinants of the sVEGF-R-2 level were age, NT-proBNP, and triglycerides. Multiple logistic regression analyses including data on age, a male gender, the body mass index, systolic and diastolic blood pressures, VEGF, sVEGF-R-1, and sVEGF-R-2 revealed that a decrease in sVEGF-R-2, but not VEGF or sVEGF-R-1, was independently associated with both LVH and systolic dysfunction.

The mitochondrial translocator protein ligands. Study of vav3 ser298thr polymorphism in patients with heart failure

The mitochondrial translocator protein ligands, 4',chlorodiazepam and TRO40303 protect cardiomyocytes against doxorubicin toxicity

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Purpose: Doxorubicin is widely used as a chemotherapeutic agent for the treatement of a large spectrum of human neoplastic diseases but its administration in humans is limited by severe cardiotoxicity. Reactive oxygen species (ROS) production and mitochondrial permeability transition pore opening (mPTP) have been identified as major events in doxorubicin-induced damage. As the mitochondrial Translocator Protein (TSPO) ligands 4',chlorodiazepam (CDZ) and TRO40303 have been shown to protect mitochondria and to reduce left ventricular dysfunction during myocardial ischemia-reperfusion through the inhibition of the opening of the mPTP, we examined their potential protective effect on doxorubicin-induced loss of contractility and ultimately on cell death in isolated adult rat cardiomyocytes.

Methods: The effects of doxorubicin (0.25-20 μM) on contractile function were evaluated in isolated adult rat cardiomyocytes paced at 1Hz by electric field stimulation. Cell viability and ROS were determined with the fluorescent probes profluorescein isothiocyanate and dichlorofluorescein, respectively. Direct mPTP opening was assessed by the intracellular calcium loading CoCl2 staining method and confirmed by the preventive effect of cyclosporin A. CDZ and TRO40303 improved cell viability, prevented the alterations of contractility and attenuation of the collapse of maximal velocities of contraction and relaxation induced by doxorubicin. The cytoprotective effect of TSPO ligands involved a high reduction of doxorubicin-induced ROS production associated with inhibition of mPTP opening as attested by the maintenance of the mitochondrial calcium fluorescence observed in the presence of CDZ or TRO40303.

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Conclusion: These data demonstrate that the TSPO ligands, CDZ and TRO40303 protect cardiac cells against doxorubicin toxicity and that this protection is at least in part mediated by prevention of ROS production and mPTP opening. Thus TSPO may represent a relevant pharmacological target for protection of the heart against doxorubicin-induced toxicity.
Conclusions: Serum levels of sVEGFR-2, but not those of VEGF or SVEGFR-1, are decreased in HF patients with LVH. sVEGFR-2 might play an active role in modulation of angiogenesis in hypertrophied LV with systolic dysfunction in humans.

Matrix metalloproteinase level can predict left ventricular remodeling and systolic dysfunction after myocardial infarction

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Purpose: Assessment of serum biomarker evidence of the early course of the cardiac type I collagen degradation (matrix metalloproteinase, MMP type -2) after myocardial infarction (MI) and relationship to left ventricular (LV) remodelling. Methods: Our study included 28 patients (14 males & 14 females with a mean age of 57.8 yrs) with acute anterior STEMI (group) and 12 healthy volunteers (7 males & 5 females with a mean age of 59 yrs) as a control group (groupII). All patients were subjected to clinical evaluation, 12-lead ECG, echodoppler study and laboratory work-up which included estimation of plasma activity level of MMP-2 within 48 h and 2 months post infarction. Echocardiography was performed within 48 h and 2 months after MI for assessment of LV volumes and ejection fraction (EF) by Simpson’s method.

Results: The mean level of MMP was higher in group I than group II (20.74 vs 1.27 mg/mL, p < 0.001). The mean EF in group I was 47.8 and 37.0 within 48 hr and 2 months post MI respectively (p < 0.017). ANOVA test was conducted to evaluate the relationship between LV systolic function and MMP level both at baseline and 2 months after MI. The mean baseline MMP was 3.19, 18.6, 24.4 mg/mL in patients with normal (EF > 55%), mild (EF = 55-54%), moderate (EF = 40-54%) and severe (EF < 40%) LV systolic dysfunction. ROC analysis revealed a cut off level of MMP > 3 mg/ml can predict the development of LV systolic dysfunction with a sensitivity of 89% and specificity of 84% respectively.

Conclusions: MMP increase after MI. The increase of MMP is associated with deterioration of LV systolic function both at baseline and 2 months later. A level >3 mg/ml can predict the development of LV systolic dysfunction with a sensitivity and specificity of 89% and 84% respectively.

Activation of agonistic proteins for toll-like receptor 4 in patients with dilated cardiomyopathy

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Background: Although there is a growing body of evidence for a potential role of the innate immune receptor Toll-like receptor 4 (TLR4) in heart failure and pharmacological antagonists are currently under investigation in clinical trials regarding inflammatory diseases, the activation cascade of this receptor in cardiac diseases is still unknown. Therefore we investigated agonistic proteins of TLR4 in blood from patients with dilated cardiomyopathy (DCM).

Methods: Classical agonistic proteins of TLR4 in blood from patients with dilated cardiomyopathy, namely lipoprotein binding protein (LBP), soluble CD14 (sCD14), lipopolysaccharide (LPS) and MD-2, were quantified in serum from 158 patients with early stage of DCM (disease duration ≤1 year, LV EF<50%, LV end-diastolic diameter > 60 mm) by ELISA. Other reasons for heart failure were excluded by coronary angiography, myocardial biopsy and echocardiography. Healthy blood donors served as controls (n=13). Protein contents of LPS were significantly reduced in patients with DCM (p > 0.05) when compared to healthy controls. In contrast, protein level of LBP (>78%, p > 0.05) and sCD14 (>19%, p < 0.001) were significantly decreased in DCM patients when compared to controls. MD-2 serum protein level were increased in direction in DCM patients when compared to healthy controls, but it did not reach a statistically significant value (p=0.06).

Conclusion: In a carefully characterised cohort of DCM patients, we showed for the first time the activation of TLR4 agonists on protein level suggest- ing a potential role of TLR4 in DCM. Our findings might give a basis of further therapeutic approaches.

Oxidative stress, inflammation and low levels of apelin as risk factors of left ventricular hypertrophy in type 2 diabetes with renal disease


Introduction: The pathophysiology of left ventricular hypertrophy is multifactorial and not completely understood. Recent studies have demonstrated the role of oxidative stress, inflammation and apelin in cardiovascular morbidity and mortality.

Purpose: The aim of this study was to evaluate factors associated with the left ventricular hypertrophy (LVH) in a population of type 2 diabetics with mild and moderate kidney disease.

Methods: In this cross- sectional study we included 78 type 2 diabetic patients (f = 39, m = 39; with a mean age of 61 years and a mean estimated glomerular filtration rate (MDRD) of 43.5 ml/min, followed in our outpatient nephrology clinic. We analyzed several laboratory parameters, such as: interleukin 6 (IL6), adiponectin (visfatin, resistin, apelin-36), oxidative stress (oxLDL), as well as the left ventricular mass index (LVMI) in our patients.

Results: In a simple regression model, the LVMI was positively correlated with age (r = 0.322, p = 0.004), IL6 (r = 0.727, p = 0.0001), oxidative stress (IL6 > 20 ng/mL, p = 0.035), LVMI (r = 0.770 p = 0.0001) and inversely with apelin-36 (r = -0.901, p < 0.0001) and the glomerular filtration rate (r = -0.381 p < 0.0001). In a multiple regression model, only IL6 (r = -0.418, p = 0.049), oxLDL (r = -0.267 p = 0.024) and apelin-36 (r = -0.736 p = 0.0001) independently influenced the LVMI.

Conclusion: Our study showed that in type 2 diabetic patients with nephropathy, the oxidative stress, the inflammation and the adiponectins are determinants of left ventricular hypertrophy. Surely they also contribute to the complexity of CKD associated cardiovascular risk.

Cardiomyocyte structural deterioration and metabolic response in human DCM hearts

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Dilated cardiomyopathy (DCM) is associated with cardiac dysfunction and various histopathological characteristic and poorly known metabolic deterioration during structural and functional remodeling. The aim of this study was the expression pattern of structural deterioration and metabolic responses in human DCM hearts. The archive tissue samples of left ventricle originated from DCM hearts divided in respect to ≤EF of three groups: (1) 45-55% (n=13), (2) 30-40% (n=8) and (3) <30% (n=10). We investigated histopathologically, ultrastructurally, histochemically by PAS staining and immunohistochemically with antibodies anti- desmin, PPARalpha, SMA alpha and caspase-3, then quantified by morphometric methods.

Conclusions: Our study showed that in type 2 diabetic patients with nephropathy, the oxidative stress, the inflammation and the adiponectins are determinants of left ventricular hypertrophy. Surely they also contribute to the complexity of CKD associated cardiovascular risk.

Abrogation of S100B expression in S100A1 deficient mice improves survival post myocardial infarction

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Post-myocardial infarction (MI) ventricular remodeling involves ventricular dilatation, hypertrophy of non-infarcted myocardium, myocyte apoptosis, the induction of S100B and the downregulation of S100A1. Whereas S100A1 deficiency results in cardiac functional impairment and high early mortality post-MI, abrogation of S100B preserves cardiac function in the setting of augmented hypertrophy post-MI. To assess the consequences of S100B expression in S100A1 knockout (KO) mice, wild-type (WT), S100A1 KO, S100B KO and S100A1 +B KO mice. Eight week-old mice were subjected to 35 days after left anterior descending coronary artery ligation with same age-matched sham-operated controls. S100A1+B KO mice demonstrated better survival as compared to S100A1 KO and WT mice.
(79.5% vs. 28.6% vs. 69.7% respectively, p < 0.05), comparable to S100B KO mice (82.6%). Most of the deaths in S100A1 KO mice occurred 3-6 days following MI. Acute hemodynamic monitoring post-MI demonstrated that the S100A1 KO animals died of rapidly progressive pump failure. At day 2 post-MI, S100A1 KO mice demonstrated S100B expression, increased left ventricular dilatation by echocardiography, less collagen I and III mRNA within the infarct area, an increased MMP-9 expression and apoptosis (as assessed by Caspase-3 activity and TUNEL staining) in the infarct border zone versus WT. Among survivors at day 35, post mortem examination indicated that the WT and KO groups of infarcted mice mounted a hypertensive response that was augmented in the S100A1 KO and S100A1-B KO groups (WT 3.95±0.21; S100A1 KO 4.05±0.13; S100B KO 4.39±0.18; S100A1-B KO 4.71±0.21 mg/mg Body Weight, p < 0.05 S100A1-B KO vs. S100A1 KO). The post infarct left ventricular end diastolic pressure was lower in S100A1-B KO and S100B KO mice compared to WT and S100A1 KO mice (S100A1-B KO 6.1±0.4 vs. S100A1KO 12.1±1.9 mmHg, p < 0.05). Our results suggest that the abrogation of S100B expression in S100A1-B KO mice augmented hypertrophy, decreased apoptosis, preserved extracellular matrix proteins and was beneficial to the preservation of cardiac function and survival within this time frame.

**Conclusions:** In patients with cardiovascular risk factors, the PPARGC1A Gly482Ser polymorphism contributes to LV hypertrophy and diastolic dysfunction with the Ser allele promoting these abnormalities.

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**Impact of the PPARGC1A Gly482Ser polymorphism on left ventricular structural and functional abnormalities in patients with cardiovascular risk factors**

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The Gly482Ser polymorphism in peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PPARGC1A) has been demonstrated to be involved in some pathophysiological aspects of metabolic and hemodynamic regulation, however the exact data linking these genomic variations with cardiac derangements are incomplete. We sought to investigate the association between the PPARGC1A Gly482Ser polymorphism and left ventricular (LV) structural and functional abnormalities in patients with cardiovascular risk factors: hypertension, diabetes, and obesity.

**Methods:** Each of 150 enrollees (age 59.8 yrs) underwent echo study with assessment of LV systolic (strain and strain rate, SR) and diastolic function (mitral inflow E/A ratio), as well as tissue e velocity (E Em), and myocardial reflectivity (calibrated integrated backscatter, diB), and evaluation of the PPARGC1A Gly482Ser polymorphism.

**Results:** Patients with the Ser allele (Ser/Ser or Ser/Gly) showed a greater extent of LV hypertrophy and LV diastolic function impairment lower LV ejection fraction and mitral E/A ratio compared with subjects with the Gly allele. No differences between these groups in metabolic control parameters (fasting glucose, HOMA IR and Hba1C), as well as in blood pressure were noted. Multivariable analysis showed the independent correlates of LV mass index were hypertension (β=0.31,p<0.001), Ser allele (p=0.32,p<0.001), Hba1C (β=0.25,p<0.001), BMI (β=0.25,p<0.001) and patient age (β=0.22,p<0.004). Em velocity was independently associated with age (β=0.22,p<0.004), Hba1C (β=0.25,p<0.002), diB (β=0.22,p<0.006), hypertension (β=0.21,p<0.008), and Ser allele (β=0.19,p<0.02).

**Conclusions:** In patients with cardiovascular risk factors, the PPARGC1A Gly482Ser polymorphism contributes to LV hypertrophy and diastolic dysfunction with the Ser allele promoting these abnormalities.
fined as death of all causes, heart transplantation, rhythm events, and heart failure-related rehospitalization.

**Results:** Gremlin-1 expression was significantly enhanced in patients with structural myocardial disease. The left ventricular function in patients with positive Gremlin-1 staining was significantly reduced compared to patients with negative Gremlin-1 staining (39.4 ± 13.8 vs. 48.0% ± 14.5, p < 0.001). Furthermore, they showed a significantly enlarged left ventricle (53.1 mm ± 10.2 vs. 48.9 mm ± 9.0, p = 0.030) and higher serum levels of C-reactive protein (1.8 mg/dL ± 3.7 vs. 1.0 mg/dL ± 1.7, p = 0.015).

**Conclusions:** Expression of Gremlin-1 is significantly enhanced in patients with structural myocardial disease. Besides TnI and NT-proBNP class ≥ III, Gremlin-1 is an independent predictor of clinical outcome.

**PREDICTORS FOR OUTCOME**

**Lung ultrasound for the evaluation of pulmonary congestion in a pre-transplantation heart failure outpatient clinic: comparison with natriuretic peptides**

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**Purpose:** Evaluation of pulmonary congestion is a frequent diagnostic challenge even by highly skilled clinicians. Recently, lung ultrasound (LUS) has been proposed for a reliable, easy evaluation of pulmonary congestion, by assessment of B-lines (also called ultrasound lungcomets). Our aim was to define the relationship between B-lines and natriuretic peptides (NT-proBNP) as part of the evaluation of pre-transplant heart failure (HF) patient in an outpatient clinic.

**Methods:** Fifty-eight patients admitted to a pre-transplantation clinic due to advanced systolic HF (65.5% men, mean age 49 ± 11 yrs, 47.2% with idiopathic and 29.3% with post-ischaemic cardiomyopathy) were enrolled. Clinical assessment, NT-proBNP analysis and LUS evaluation were independently performed.

**Results:** Feasibility was 100%. Mean time toperform LUS was 9.91 ± 1.24 minutes. Significant pulmonary congestion was present in 57.9% by LUS (total B-lines number ≥ 15). B-lines number was significantly correlated to NT-proBNP values (r = 0.74, p < 0.001). Assuming NT-proBNP > 1000 ng/mL as a reference for decompensated HF, ROC analysis showed a C statistic of 0.88 (95% CI: 0.72-0.92, p < 0.0001) for LUS, providing the best accuracy with a cut-off of 14 B-lines (sensitivity 96.2, specificity 71.9%).

**Conclusion:** In a pre-transplantation heart failure outpatient clinic, B-lines evaluated by LUS are significantly correlated to NT-proBNP. Given its accuracy, low cost and portability, LUS may be considered as a reliable tool for a quick and easy evaluation of pulmonary congestion in decompensated HF patients.

**Depressed midwall fractional shortening is a powerful prognostic determinant in cardiac AL amyloidosis**

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**Purpose:** Systemic amyloidoses are characterized by extracellular deposition of insoluble fibrils in various tissues. Clinical presentation is variable, depending on the extension of deposits and on the extent of organ dysfunction. In AL amyloidosis, the amyloidogenic protein is an immunoglobulin light chain or a fragment of an Ig light chain that is synthesized by clonal plasma cells in bone marrow. Cardiac involvement is not only frequent, but it is also the most common cause of death. Cardiac amyloidosis represents an archetypal form of restrictive heart disease, characterized by profound diastolic dysfunction. Since ejection fraction is preserved until the late stage of the disease, the majority of patients with cardiac AL amyloidosis do fulfill the definition of diastolic heart failure, i.e. heart failure with preserved ejection fraction. In another clinical model of diastolic heart failure, i.e. pressure-overload left ventricular hypertrophy, depressed midwall fractional shortening (i.e. a marker of myocardial contractile dysfunction) has been shown to be a powerful prognostic factor.

**Method:** To assess a potential prognostic role of midwall fractional shortening in cardiac AL amyloidosis patients, we enrolled 21 consecutive echocardiographic evaluation as well as NT-proBNP determination at diagnosis. Patients with ejection fraction below 50% (n = 28) were excluded. Prognosis was assessed after a median follow-up of 561 days.

**Results:** When compared with AL patients without myocardial involvement, cardiac AL was characterized by increased wall thickness (p < 0.001) and reduced end-diastolic LV volumes (p < 0.001). As expected, diastolic dysfunction was evident in all cardiac AL patients, as evidenced by increased E/E’ ratio (p < 0.001). Midwall fractional shortening was markedly depressed (11.2 ± 4.3 vs 22.1 ± 4.4%, p < 0.001), despite preserved ejection fraction. At multivariable analysis, midwall fractional shortening (p < 0.0003) and NT-proBNP (p < 0.0002) were the only significant prognostic determinants, whereas other indices of diastolic (E/E’ ratio, transmural and pulmonary vein flow velocities) and systolic function (tissue-Doppler systolic indices, ejection fraction) did not enter the model.

**Conclusions:** In cardiac AL amyloidosis with normal ejection fraction, depressed midwall fractional shortening, a marker of myocardial contractile dysfunction, is a powerful predictor of survival.

**The electrocardiographic/echocardiographic mass ratio in the diagnosis of cardiac amyloidosis**

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**Background and Aim:** In cardiac AL amyloidosis the increase in wall thickness caused by extracellular amyloid deposition leads to marked increases in left ventricular (LV) mass. At variance with other forms of cardiac hypertrophy, this is often associated with abnormally low electrocardiographic (ECG) voltages, due to amyloid negative effects on intracardiac electrical conduction. Although such a discrepancy (low ECG “electrical” LV mass/high echo-derived LV mass) might be a powerful diagnostic clue, this is often missed since almost 40% of cardiac AL patients do not strictly fulfill the definition of “ECG low voltages” (< 5 mV in all peripheral leads).

**Methods:** To evaluate its possible clinical relevance, an index of the ECG/echo mass ratio was computed and divided by echo-derived LV mass. In patients with other potential causes of low QRS voltages (e.g. large pericardial effusions, obesity, chronic obstructive lung disease, and severe peripheral edema) were excluded.

**Results:** In a preliminary evaluation of 50 patients, the LV mass ratio showed a 91.43% sensitivity and a 74.53% specificity in identifying the presence of cardiac involvement in 145 out of 200 consecutive AL patients. When compared to both hypertrophic cardiomyopathy (0.37 ± 0.30-0.53 mV/g/m²) and hypertensive (0.33 ± 0.27-0.40 mV/g/m²) subjects, the ECG/Echo mass ratio was markedly decreased in patients with cardiac AL (0.14 ± 0.10-0.20 mV/g/m²), p < 0.001 vs. all the other groups). The area under the ROC curve for the detection of cardiac AL involvement was high: 0.970 (95% CI, 0.956 to 0.980, p < 0.001).

**Figure 1. ROC Curve - B-lines number**

**Conclusion:** In a pre-transplantation heart failure outpatient clinic, B-lines evaluated by LUS are significantly correlated to NT-proBNP. Given its accuracy, low cost and portability, LUS may be considered as a reliable tool for a quick and easy evaluation of pulmonary congestion in decompensated HF patients.

**Depressed midwall fractional shortening is a powerful prognostic determinant in cardiac AL amyloidosis**

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**Purpose:** Evaluation of pulmonary congestion is a frequent diagnostic challenge even by highly skilled clinicians. Recently, lung ultrasound (LUS) has been proposed for a reliable, easy evaluation of pulmonary congestion, by assessment of B-lines (also called ultrasound lungcomets). Our aim was to define the relationship between B-lines and natriuretic peptides (NT-proBNP) as part of the evaluation of pre-transplant heart failure (HF) patient in an outpatient clinic.

**Methods:** Fifty-eight patients admitted to a pre-transplantation clinic due to advanced systolic HF (65.5% men, mean age 49 ± 11 yrs, 47.2% with idiopathic and 29.3% with post-ischaemic cardiomyopathy) were enrolled. Clinical assessment, NT-proBNP analysis and LUS evaluation were independently performed.

**Results:** Feasibility was 100%. Mean time to perform LUS was 9.91 ± 1.24 minutes. Significant pulmonary congestion was present in 57.9% by LUS (total B-lines number ≥ 15). B-lines number was significantly correlated to NT-proBNP values (r = 0.74, p < 0.001). Assuming NT-proBNP > 1000 ng/mL as a reference for decompensated HF, ROC analysis showed a C statistic of 0.88 (95% CI: 0.72-0.92, p < 0.0001) for LUS, providing the best accuracy with a cut-off of 14 B-lines (sensitivity 96.2, specificity 71.9%).

**Conclusion:** In a pre-transplantation heart failure outpatient clinic, B-lines evaluated by LUS are significantly correlated to NT-proBNP. Given its accuracy, low cost and portability, LUS may be considered as a reliable tool for a quick and easy evaluation of pulmonary congestion in decompensated HF patients.
Evidence of subclinical perimyocardial involvement in patients with systemic lupus erythematosus: late gadolinium enhancement study

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Purpose: Increased inflammation has been linked to myocardial dysfunction and heart failure. We investigated whether patients with systemic inflammatory diseases, such as systemic lupus erythematosus (SLE), free of cardiac symptoms, have evidence of subclinical inflammatory myocardial involvement.

Methods and results: A total of 27 SLE patients (male=0, mean age 41±11 years) with no previous cardiac history underwent cardiovascular magnetic resonance imaging for assessment of function and late gadolinium enhancement on a 3 Tesla scanner. In these patients, the presence of significant coronary artery disease was excluded by virtue of negative adenosine myocardial perfusion or normal high-resolution magnetic resonance coronary angiography. Fifteen age-matched subjects with a low pre-test probability acted as a control group. In SLE group, there was deceased global systolic function (SLE vs. controls: 47.7±5% vs. 50.2±5%, p<0.05) and increased LV mass index (68.2±4 g/m² vs. 43.4±3 g/m², p<0.001). Late gadolinium enhancement was seen in 20 SLE subjects: 14 patchy areas of intramyocardial enhancement and 6 subjects showed intromyocardial stria. Myocardial enhancement was invariably affecting the basal segments of inferior septum, inferior and inferolateral walls and right-ventricular insertion points. None of the subjects showed regional myocardial fibrosis. Pericardial effusion was present in 4 patients. Pericardial enhancement was present in 17 patients (5 of these had no myocardial enhancement), enveloping globally right and left ventricle, with mean thickness of the pericardial space along the free LV wall of 3.1±0.7 mm.

Conclusions: We demonstrate that in SLE patients free of significant coronary artery disease there is evidence of subclinical perimyocardial involvement.

Cardiac myosin binding protein C gene polymorphisms and diastolic heart failure

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Objective: Myosin binding protein C (MYBPC) plays a role in ventricular relaxation. The aim of the study was to investigate the association between cardiac myosin binding protein C (MYBPC3) gene polymorphisms and diastolic heart failure (DHF) in a human case-control study.

Methods: A total of 352 participants of 1752 consecutive patients from the National University Hospital and its affiliated hospital were enrolled. 176 patients diagnosed with DHF confirmed by echocardiography were recruited. Controls were matched 1:1 by age, sex, hypertension, diabetes, renal function and medication use. We genotyped 12 single nucleotide polymorphisms (SNPs) according to HapMap Han Chinese Beijing databank across a 40 kb genetic region containing the MYBPC3 gene and the neighboring DNA sequences to capture 100% of haplotype variance in all SNPs with minor allele frequencies ≥5%. We also analyzed associations of SNPs and haplotypes with DHF and linkage disequilibrium (LD) structure of the MYBPC3 gene.

Results: In a single locus analysis, SNP rs2290149 was associated with DHF (allele-specific p = 0.004; permuted p = 0.031). The SNP with a minor allele frequency of 9.4%, had an odds ratio 2.14 (95% CI 1.25-3.66; p = 0.004) for the additive model and 2.06 for the autosomal dominant model (GG+GA, AA, 95% CI 1.17-3.63; p = 0.013), corresponding to a population attributable risk fraction of 12.02%. The haplotypes in a LD block of rs2290149 (C-C-G-G) was also significantly associated with DHF (odds ratio 2.10 (1.53 – 2.89); permuted p = 0.029).

Conclusions: We identified risk-conferring genetic variants of MYBPC3 gene for DHF in a Chinese population.

Subclinical abnormalities of the arterial tree and left ventricular myocardial deformation, relaxation and twist in chronic kidney disease

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Purpose: Chronic kidney disease (CKD) associates with adverse cardiovascular outcomes. However, the disadvantageous effects of renal dysfunction on left ventricular systolic and diastolic function remain unclear. The objective of this study was to look at the effect of CKD on (i) left ventricular (LV) systolic and diastolic strain patterns and LV twist with the use of conventional and 2D speckle tracking echocardiography, and (ii) arterial stiffness as measured by pulse wave velocity (PWV).

Methods: Seventy-four chronic kidney disease patients were assessed using conventional, 2D speckle tracking echocardiography (EchoPAC-GE) and applanation tonometry (Sphygmocor). Patients with (i) LV systolic dysfunction or regional wall motion abnormalities, (ii) moderate to severe valvular disease or (iii) heart rhythm other than sinus were excluded (N=5). Global systolic strain (GS) and strain rate (GSRs), early (GSRe) and late (GSRd) diastolic longitudinal strain rate, 17 twist and twist rate, mitral inflow, tissue PW–Doppler velocities and PWV were recorded.

Results: The mean age of CKD patients was 54±15.4 years and 34 (49.3%) were females. Mean baseline LV ejection fraction (EF) was 62.3±5.4%. Six (8.7%) patients were stage 1 CKD, 17 (24.6%) stage 2, 29 (42%) stage 3, 12 (17.4%) stage 4 and 5 (7.2%) stage 5. Estimated Glomerular Filtration Rate (eGFR) correlated significantly with PWV (r=0.37, p=0.05) and GSRd (r=0.269, p=0.028), LV twist rate (r=0.275, p=0.026) and E/E’ ratio (r=0.370, p=0.002). There was no correlation between eGFR and GSRe. A significant reduction with worsening eGFR whereas LV filling pressure and twist rate appear to increase, compensating for the impaired diastolic filling. Outcome studies may be required to identify the association of these early markers of cardiovascular disease in CKD patients.

Peak cardiac power output: a new hemodynamic tool to aid the diagnosis of heart failure with preserved ejection fraction? A pilot study

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Purpose: By coupling both the pressure and flow generating capacities of the heart, the peak cardiac power output peak (CPO) is a direct measure of cardiac function during exercise and a major determinant of exercise capacity. Furthermore, in patients with systolic heart failure (SHF), peak CPO < 1.5 W is an independent and powerful predictor of prognosis that can be measured non-invasively using cardio-pulmonary exercise testing. This is the first study to investigate the diagnostic value of the CPO in patients with heart failure with preserved ejection fraction (HFpEF).

Methods: Among the 45 patients (age 66 [53-73] years) included into the study, 10 subjects were classified as HFpEF, 24 patients had SHF (EF < 35%) and 11 subjects served as a control group. All subjects underwent symptom limited bicycle exercise with noninvasive quantification of cardiac output (CO) using an inert gas rebreathing method. CPO was calculated as the product of CO and mean arterial blood pressure×451 as described previously.

Results: The peak CPO was significantly different among the groups: 2.42 (1.88-3.86) W in controls vs. 1.67 (1.17-2.09) W in SHF vs. 1.44 (1.22-1.69) W in HFpEF (p=0.018). There was a significant correlation between the peak CPO and the peak oxygen uptake (VO2peak; n=0.455, p=0.002) and NT-proBNP levels (n=0.585, p=0.001).

Conclusion: The present study is the first to evaluate peak CPO as a direct measurement of hemodynamic response to exercise in patients with HFpEF. The peak CPO of patients with HFpEF and SHF was similar reduced. Therefore, peak CPO can identify abnormalities in cardiovascular function consistent with those
predicting mortality in HFpEF and may enhance the ability to accurately identify patients at greatest risk for heart failure related complications.

P5147  Relationship of pro-collagen biomarkers of myocardial fibrosis with myocardial dysfunction and metabolic derangement in type 2 diabetes

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Purpose: Myocardial fibrosis is a potential contributor to non-ischemic diastolic dysfunction (DD) in type 2 diabetes (T2DM). We sought the relationship between fibrosis markers, myocardial dysfunction and metabolic derangement.

Methods: Clinical, imaging and biochemical data were measured in 390 asymptomatic subjects (216 men, 58±10 yrs) with T2DM. Myocardial function was examined with standard 2D echo, early diastolic (em) and systolic velocity, strain, strain rate, and backscatter (ciB). Amino-terminal propeptides of pro-collagen type I (PINP) and type III (PIIINP) were measured by radio-immunoassay, and the cardiac-tissue terminal propeptide of type II (P IPCC) was measured by enzyme linked-immunoassay.

Results: Patients were stratified by metabolic derangement; 53 (14%) had isolated T2DM, 67 (17%) had T2DM with isolated hypertension, 178 (45%) had T2DM with non-isolated metabolic syndrome and 92 (24%) had T2DM with type 2 diabetes and end-organ involvement (microalbuminuria). Progressive metabolic derangement was mirrored by worse DD (em < p=0.001), increased ciB (p=0.016), greater insulin resistance (log HOMA-IR < p=0.001) and worse exercise capacity (VO2 max < p=0.001) but only a trend towards proportionally higher PIIINP levels. PIIINP (3.9±1.9 μg/L) was associated with insulin resistance (log HOMA-IR < p=0.206, p<0.008) independent of age (p=0.186, p=0.017) and renal function (creatinine > p=0.227, p=0.004). PINP (42.2±8.4 μg/L) and PCIP (275±90.4 ng/ml) were not associated with metabolic parameters or myocardial properties.

Conclusions: Metabolic derangement in T2DM is proportionally associated with worsening DD and increased myocardial signal intensity (ciB). The association with PIIINP levels is weak, suggesting a limited role of type III collagen turnover in subclinical, non-ischemic diabetic heart disease.

P5148  Acute improvement of left atrial mechanics and left ventricular diastolic function after Transcatheter Aortic Valve Implantation

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Purpose: Aortic stenosis leads to remodelling of the left ventricle and atrium that causes systolic and diastolic dysfunction. Transcatheter aortic valve implantation (TAVI) is a rapidly evolving therapy for severe aortic stenosis in high-risk patients. Two-dimensional speckle tracking echocardiography (STE)-derived strain measurements enable the regional assessment of left atrial (LA) mechanics. The goal of this study was to describe the acute effects on myocardial deformation of the LA and left ventricular (LV) diastolic function after TAVI.

Methods: 32 consecutive patients (17 female, mean age 76 years, mean Euroscore 18.7%, mean LVEF 52.5±15.7%) with severe aortic stenosis (0.73±0.19 cm2) were enrolled into our study. We performed transhoracic echocardiography including STE of the basal septal segment of the left atrium to determine peak systolic strain (LAps), strain during early diastole (LaEAD) and, if feasible, strain during atrial contraction (LAa) representing LA reservoir, conduit, and contractile function, respectively. In addition, the corresponding strain rate values such as systolic atrial strain rate (SSr), early diastolic atrial strain rate (ESr), and late diastolic atrial strain rate (Asr) were analysed. Diastolic assessment of the left ventricle included standard indices and the atrial fraction. LA volumes throughout the cardiac cycle were also assessed.

Results: At baseline, 24 (75%) of our patients were in sinus rhythm. Heart rate (HR) and blood pressure were unchanged compared to baseline and after one week did not differ significantly. The atrial reservoir (LAps) and conduit function (LAps + LEd) improved significantly (19.2±12.0% vs. 24.9±16.2%, P < 0.02 and 9.8±6.9% vs. 14.7±8.3%, P < 0.009, respectively). There was a significant reduction of the decrement of the deceleration time (DT) (257±88 vs. 188±71 ms, P < 0.001) and an improvement of pw-tissue Doppler derived E'/Em (5.7±1.1 vs. 7.3±2.3 cm/s, P < 0.003). In contrast, there was no improvement in atrial contraction; contractile function (E'Em - LAA, 12.1±8% vs. 14.6±11.8% < P = 0.4), A'Em (8.6±3.1 cm/s vs. 6.3±2.6 cm/s, P = 0.25) and atrial fraction (0.37±0.14 vs. 0.34±0.13 < P = 0.78). In addition, E/E' and the LA diastolic volume (42.3±15.1 ml/m2 vs. 39.0±15.1 ml/m2, P = n.s.) did not differ significantly.

Conclusion: One week after TAVI only the reservoir and conduit function of the left atrium improved, whereas the late diastolic LA contraction and the LA volume were unchanged. This was accompanied by improvement of the early LV diastolic function indicating acute recovery of LV relaxation and LA function.

P5149  Diagnostic value of pulsatile hemodynamics for heart failure with normal ejection fraction

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Purpose: Increased arterial stiffness and wave reflections are present in most patients with heart failure with normal ejection fraction (HFNEF). We tested whether measurements of pulsatile arterial function are useful for diagnosing HFNEF, in comparison with and in addition to Tissue Doppler Echocardiography (TDE).

Methods: Patients with dyspnea as leading symptom were categorized as having HFNEF or no HFNEF; based on invasively derived filling pressures and natriuretic peptide levels. Pulse wave velocity was measured invasively (aPWV), aortic pulse pressure (aPP) and its components (incident pressure wave front = P1, forward wave amplitude = Pi, augmented pressure = AP, backward wave amplitude = PiB) were quantified non-invasively from radial tonometry, using pulse waveform analysis and wave separation analysis. Results: 71 patients were classified as having HFNEF, and 65 as no HFNEF (in 223 patients, intermediate results were present). Patients with HFNEF were older, more often had hypertension and diabetes, and had more advanced coronary artery disease, larger left atria and higher left ventricular mass; blood pressures and all measures of arterial stiffness and wave reflections were higher in HFNEF group. Receiver operating curve analysis derived area under the curve values were 0.923 for E'/Em (medial annulus), the best TDE parameter, and 0.867, 0.851, 0.812, 0.813, 0.854, and 0.825 for aPWV, aPP, Pi, AP, and PiB, respectively (Figure). Multivariable logistic regression models proved that measures of pulsatile arterial function provided independent and additive diagnostic information.

Conclusion: Measures of arterial stiffness, central pressures and wave reflections complement TDE for the diagnosis of DHF.

P5150  Perhexiline corrects energy deficiency and improves symptoms in chronic heart failure

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Background: We hypothesized that the metabolic modulator perhexiline would ameliorate myocardial energy deficiency and improve symptoms in dilated cardiomyopathy.

Methods and Results: 50 patients with heart failure (NYHA II - IV, LVEF -40%) were randomised to 100mg bd (n=25) or placebo (n=25) for 1 month in a double blind fashion. Myocardial ratio of phosphocreatine to adenosine triphosphate, an established marker of cardiac energetics status, as measured by 31P magnetic resonance spectroscopy, echocardiography, symptoms and quality of life scores were assessed at baseline and at study end. Perhexiline improved the primary
We hypothesised that levosimendan will improve myocardial regional contractility without harmful side effects in acute PCI treated STEMI patients complicated by decompensated heart failure.

**Method:** Patients developing clinical signs of heart failure (including cardiogenic shock) within 48 hours after a primary PCI treated STEMI, with decreased wall-motion in ≥3 of 16 segments evaluated by echocardiography, were randomised to a 216-hour levosimendan infusion or matching placebo in a double-blind design. Primary endpoint was change in wall-motion score index (WMSI) from baseline to day 5. Infarct size was measured by single photon emission computed tomography (gated SPECT) at 6 weeks.

**Results:** (mean ±SD): A total of 61 patients were included. Age (64±13 years), peak cardiac troponin T (3083±6996 ng/l), BP (104/66 mmHg) and left ventricular EF (42±9%) at inclusion, were not significantly different between groups. Infarct size at 6 weeks (42±16%) was similar in both groups. There was significantly larger improvement in WMSI from baseline to day 5 in the levosimendan group compared to placebo from (1.94±0.20 to 1.66±0.31 vs 2.02±0.26 to 1.83±0.26 respectively, p=0.03). There were no significant between-group-differences from baseline to day 5 in changes in NT-proBNP levels, a clinical composite score, frequency of atrial fibrillation or ventricular arrhythmia, new ischaemic episodes or use of inotropy as rescue therapy. There were significantly more episodes of hypotension during study drug infusion in the levosimendan group (63% vs 36%, p=0.03), but no difference in blood pressure at the end of infusion or in use of vasopressors. One patient died in the levosimendan group and 4 patients in the placebo group during 6 months follow-up. No significant between-group-differences at 6 months in MACE (death, nonfatal myocardial infarction or revascularisation of the infarct related artery) or in rehospitalisation for heart failure, were present.

**Conclusion:** Levosimendan treatment improved regional contractility measured by WMSI in patients with acute PCI treated STEMI complicated by heart failure, but did not affect NT-proBNP levels or clinical symptom score. The treatment was well tolerated without any increase in atrial fibrillation or ventricular arrhythmias.
Acute heart failure patients with high initial blood pressure shows paradoxical hemococoncentration on admission

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Introduction: As volume overload is a major profile of acute heart failure syncope (AHHF), diuretics, as well as oxygen, nitrites, and morphine, are a mainstay of therapeutic strategy for those patients. Though decongestion/diuretic therapy are started immediately after admission in most of patients, changes in concentration of blood components in this period remain to be investigated.

Method: We studied 135 patients admitted to our hospital with symptoms of AHHF between January and December 2010. Changes in hemoglobin levels between on admission and 24-12 hours postadmission were evaluated. Patients with cardiogenic shock, heomodilution, blood transfusion, and/or urgent coronary angiography were excluded.

Results: In spite of decongestion/diuretic therapy started immediately after admission, hemoglobin level on admission was paradoxically higher than the level of 24-12 hours postadmission in 95 patients (70%). Patients in the top tertile of baseline-to-24h decrease of hemoglobin (ΔHb) were defined to have an evidence of admission hemococoncentration. The ΔHb in patients with admission hemococoncentration was 1.8±0.7 g/dL (12.5±2.5 g/dL) on admission and 11.6±2.4 g/dL at 24h (p=0.001). However, 0.8±0.7 g/dL in patients with higher initial systolic blood pressure (SBP; >140 mmHg) than lower SBP (45% vs. 16%, p=0.001). Furthermore, ΔHb was positively and significantly correlated not only with initial SBP (r=0.43, p<0.001) but also initial heart rate (r=0.28, p=0.001), suggesting sympathetically mediated fluid shifts between extracellular and circulating volume under the development of AHHF.

Conclusion: AHFS patients with high initial SBP shows paradoxical hemococoncentration on admission. Sympathetically mediated fluid shifts between extracellular and circulating volume may underlie the development of AHFS.

Myocardial and vascular dysfunction in young subjects, are related to dyslipidaemia and abdominal obesity but not to glycaemia

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Purpose: To investigate the relationships between cardiovascular risk factors and subclinical myocardial and vascular dysfunction in young adults.

Methods: We recruited 53 young subjects under 30 years of age including 34 healthy volunteers (mean age 24±1.2 years) and 19 subjects with type 1 diabetes mellitus (mean age of 21±1.36 years, mean duration of diabetes 9.0±7.5 years; mean HbA1c 8.8±1.6%).

Correlates of arterial stiffness (n=53)

Lateral a’ (r, p) -0.45, 0004* 0.38, 0.02* -0.41, 0.009 Medial a’ (r, p) -0.17, 0.32 0.37, 0.01 -0.34, 0.004

Lateral a’ (r, p) -0.45, 0004* 0.38, 0.02* -0.41, 0.009 Medial a’ (r, p) -0.17, 0.32 0.37, 0.01 -0.34, 0.004

Conclusions: In young adults, abdominal obesity and dyslipidaemia may be more important risk factors for early myocardial and vascular dysfunction than is glycaemia.

Which adjunctive test to clinical evaluation is better to diagnose pulmonary congestion in a pre-transplantation heart failure outpatient clinic?


Purpose: Patients with heart failure (HF) are often evaluated with some degree of uncertainty, even by highly skilled clinicians. Optimal evaluation includes balance of symptoms, physical examination and adjunctive testing. Our aim was to define more clearly the relationship between B-lines assessed by lung ultrasound (LUS), chest x-ray (CXR), clinical congestion score (CCS) and the natriuretic peptides

Predictors for outcome
Sonographic pulmonary comet sign in diagnosis and monitoring of pulmonary congestion in HF

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Background and Aim: Pulmonary congestion is useful marker of decompensated HF. The aim was to study the importance of Lungs “Comet tail” artefact in diagnosis and monitoring of Pulmonary Congestion in patients with different types Heart Failure.

Methods: We studied 430 patients with II-IV NYHA class HF. 338 Patients have Systolic HF (SHF), 92 patient – HF with preserved systolic function (DHF), 70 patients with chronic obstructive pulmonary disease (COPD) and 155 patients with heart diseases but without HF (control). Sonographic evaluation of a lung was done in horizontal or vertical positions of patient, from 10 points of thoracic wall which corresponded to the projection lung lobes.

Results: In patients with CHF we significantly often found the “Comet Tail” artefact in diagnosis and monitoring of Pulmonary Congestion in patients with different types Heart Failure. The LUS feasibility was 100%. Mean radiation dose to perform LUS was 9.9±2.45 minutes. Significant congestion was present in 52.6% estimated by a clinical congestion score, 57.9% by LUS (total B-lines number ≥15), in 45.6% by NTproBNP >100pg/mL and in 43.9% by CXR evaluation. Assuming CXR as a reference for decompensated HF, ROC analysis showed a C statistic of: CCS=0.69 (95%CI: 0.55-0.83, p<0.0001), LUS B-lines number ≥15 = 0.82 (95%CI: 0.71-0.93, p<0.0001) and NTproBNP ≥ 0.81 (95%IC: 0.69-0.93, p<0.0001). When NTproBNP was assumed as a reference for decompensated HF the C statistic was: CCS=0.71 (95%CI: 0.57-0.84, p<0.0001), LUS B-lines number ≥15 = 0.88 (95%CI: 0.79-0.97, p<0.0001) and CXR=0.79 (95%: 0.66-0.91, p<0.0001).

Conclusion: Our data shows that clinical evaluation understimates the presence of pulmonary congestion. Given its accuracy, low cost, radiation free and portability, LUS may be considered as a reliable tool for quick and easy evaluation of pulmonary congestion.

P5160 Correlations between hemodynamic parameters and serum high sensitive troponin-T


Serum troponin is widely accepted as a prognostic biomarker of heart failure. However the correlation and cause of elevation of serum troponin has not been studied well.

Methods: Heart stable heart failure patients who were performed right and left heart invasive catheterization were analyzed (male 110, median age 72). Serum high sensitive troponin-T levels were compared with parameters obtained from invasive right and left catheterization.

Results: Serum high sensitive troponin-T (Roche diagnostics) were detected in all the patients (median 0.012 inter quartile range 0.007-0.021ng/ml). Stepwise regression analysis revealed age (coefficient 0.012, 95% confidence interval 0.007-0.017, p<0.0001), serum hemoglobin concentration(-0.005, [-0.016; -0.022], p=0.0045), estimated glomerular filtration rate (-0.005, [0.01-0.019], p=0.0311), ejection fraction(-0.013, [0.019-0.007], p<0.0001), left ventricular end diastolic pressure (0.015, [0.004-0.026], p=0.0092) were associated with serum high sensitive troponin-T.

Adjusted associations with troponin-T

<table>
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</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>-0.069</td>
<td>0.024</td>
<td>-0.016</td>
</tr>
<tr>
<td>gFR, ml/min/m²</td>
<td>-0.005</td>
<td>0.002</td>
<td>-0.001</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>-0.013</td>
<td>0.003</td>
<td>-0.019</td>
</tr>
<tr>
<td>Left ventricular end diastolic pressure, mmHg</td>
<td>0.015</td>
<td>0.006</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Conclusion: In heart failure patients, serum troponin-T concentration was increased by older age, anemia, impaired renal function, reduced left ventricular ejection fraction, and elevated left ventricular end diastolic pressure.

P5161 A New Radiologic Score for the verification of evolving pulmonary congestion-edema in the course of Acute Myocardial Infarction


Background: Twenty five percent of patients sustaining acute myocardial infarction (AMI) develop pulmonary congestion-edema (PEd) as a result of increased lung fluid content (LFC). There is no method to monitor a changes in LFC. Lung impedance (LI) that decreases with increasing LFC may be indicator of LFC but needs verification.

Methods: Disadvantages of this modality is patients with non-ischemic cardiomyopathy (NICM). We aimed to investigate the clinical significance of the occurrence of AHFS during the morning in NICM patients.

Methods: We have retrospectively studied consecutive 201 NICM patients admitted for AHFS. We defined the patients of AHFS, who developed their symptoms from the midnight until 8 a.m. as the morning-HF group, and the others as the control-HF group.

Results: Twenty seven patients with the occurrence of AHFS during the morning were recognized in the present study, whose characteristics were significantly higher age, increased systolic blood pressure (BP) than in the control-HF group (72±13 vs 66±16 y.o., 156±154 vs 124±28 mmHg, p<0.05). Although in- and out-of hospital mortality did not differ between the morning-HF and control-HF groups, but the rate of re-hospitalization for heart failure in the morning-HF group was significantly higher than the control-HF group. Sub-analysis using polysomnography revealed that the prevalence of sleep apnea was significantly higher in the morning-HF group compared with in the control-HF group (100% vs. 74%, p<0.05).

Conclusion: The occurrence of acute heart failure syndromes in the morning itself predicts poor clinical prognosis in association with higher age and sleep apnea, suggesting that increased sympathetic nerve activity (SNA) in the morning may play a significant role in deteriorating HF. Management to control SNA by treating sleep apnea or BP control in chronic phase would be the key to reduce the re-hospitalization for the worsening heart failure.
Predictors of augmented peripheral chemosensitivity in patients with systolic heart failure

Results: Study population included patients admitted to AMI, with no radiological and clinical signs of PE at admission. RS of 0-2 characterized patients with no lung edema, 3-4 with interstitial edema, a 5-6 mild alveolar lung edema, and 7-8 and 9-10 signified moderate and severe alveolar edema. Patients were undergone to 96 hrs of monitoring. 2237 X-rays were done. 480 of 636 patients did not develop PE (CS0). Their RS was 0.3±0.5 at the beginning. Maximal decrease of LI from initial during monitoring in this group was 6.3±6.1% (p<0.001). At this time RS was 1.3±1.2 (p<0.01). 156 patients developed PE. At CS1 (rates at lung bases) RS was 5.2±0.9 (p<0.001) and LI decreased by 21.9±5.2% (p<0.001). At CS2 (rates at low half lung) and 3(rates over all lung), RS were 6.9±1.1 and 9.8±0.5 (p<0.001). LI decreased by 30.1±8.3% and 39.3±7.7%, respectively (p<0.001). PE4 CS corre- lated with RS (r=0.6, p<0.001) and with LI (r=0.6, p<0.001). RS correlated with LI (r=-0.9, p<0.001). Changes in RS and LI strikingly preceded the detection of lung rales.

Conclusions: RS was shown to be a simple and reliable method to assess changes in LFC in patients developing AHF and well correlated with the degree of lung congestion.

Predictors of augmented peripheral chemosensitivity revisited in 2012: a classical clinical sign.

Methods: Thirty CHF patients were studied (NYHA class II, mean LVEF 27.1±7.1%, 15 patients were self-frequenters (31%), 10 with neurogenic convert- ing enzyme inhibitor and/or angiotensin receptor blocker (38%) and aldosterone antagonist (26%). Peripheral chemosensitivity was assessed with the transient hypoxia obtained using nitrogen gas administration and expressed by the linear regression slope between SaO2 (%) and minute ventilation (l/min). Based on previ- ous experience, high peripheral chemosensitivity was defined as a response ≥ 0.7 l/min%. Statistical significance was defined at p<0.05.

Results: Thirteen (43%) CHF patients showed high chemosensitivity. The fol- lowing clinical parameters differentiated those with high vs normal chemosensi- tivity: elevated NTproBNP (453±1.2195 vs 2051.222pm/ml), lower peakVO2 (14.1±1.8 vs 18.6±6.31 ml/kg/min), shorter pulmonary acceleration time (84.2±18.8 vs. 103.167.6 ms), greater right ventricle end-diastolic diameter (33.1±10.9 vs 27.07±14.46 mm) and more frequent incidence of atrial fibrillation (69% vs 24%) (high vs normal chemosensitivity, respectively; p<0.05 in all com- parisons). Controlling for these factors, NTproBNP alone significantly predicts chemosensitivity.

Conclusions: High peripheral chemosensitivity is common in contemporary CHF patients despite optimal neurohumoral blockade. Correlation of NTproBNP, peakVO2, pulmonary acceleration time and AF with chemosensitivity suggests 1) an association between peripheral chemosensitivity and 2) that common clinical measurements might be used to screen patients for peripheral chemosensitivity. Assessment of these parameters may therefore be useful for selection of patients for novel therapies targeting peripheral chemore- ceptors.

P5162

BPN is higher in OptiVol alert with intrathoracic impedance than at baseline: from MOMOTARO study

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Background: Heart failure (HF) is one of the most common causes for hospi- tализаций. A major cause of HF related hospitalizations is fluid accumulation. Recent studies have suggested that intrathoracic impedance (ITI) may be a use- ful parameter to track daily changes in pulmonary fluid status. OptiVol alert, which is an artificial neural network using body weight, blood pressure (BP), SAT, heart rate, thoracic impedance, clinical and cardiac information, was used to detect impending fluid accumulation at an early stage. However, the sensitivity and specificity of OptiVol alert for deteriorated HF have not been sufficient for it to be a clinically useful param- eter. Therefore, we examined the relationships of OptiVol alert and ITI with various parameters.

Methods: This study was a prospective multicenter study. Patients who suffered from structural heart disease and who had been enrolled with a high energy de- vice with an OptiVol feature were included in this study. The patients underwent various examinations, including body weight, chest X-ray, electrocardiogram, a blood sample such as BNP concentration and echocardiography, at enrolment and following an OptiVol alert. We examined difference in various values between OptiVol alert and baseline. All patients were followed by a wireless remote mon- itoring system. We defined that primary endpoint was the difference of log BNP between OptiVol alert and baseline, and secondary endpoint was the difference of other parameters between OptiVol alert and baseline.

Results: From April 2010 to December 2011, 200 patients in 12 institutes were enrolled in the present study. Mean age was 65.3±12.2 years, mean ejection fraction was 44.2±14.3% and mean NTproBNP was 5.6±5.9. During a mean follow- up period of 15.3±4.2 months, we had 255 OptiVol alert events in the OptiVol threshold of 60. In primary endpoint, log BNP was higher in OptiVol alert than at baseline, but not significantly (5.2±1.1 vs 5.1±1.1, p=0.06). However, the rate of change in ITI was negatively correlated with the rate of change in log BNP (r=−0.35, p<0.01). In OptiVol alert events with ITI equal to or less than 96% of mean ITI, log BNP was significantly higher in OptiVol alert than at baseline (5.5±1.2 vs 5.2±1.0, p<0.01). In OptiVol alert events with ITI more than 96% of mean ITI, there was no significant difference in log BNP between OptiVol alert and baseline. In secondary endpoint, red blood cell, hemoglobin, hematocrit, total protein and albumin were significantly lower in OptiVol alert than at baseline.

Conclusion: OptiVol alert with decreased ITI, rather than OptiVol alert only, seems to represent fluid retention.

P5164

A classical clinical signs revised in 2012: echocardiographic assessment of jugular vein analysis from SICA-HF study

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Background: Jugular vein (JV) distension reflects the pressure in the right atrium. Clinical assessment of JV distension in patients with heart failure is a fundamental clinical sign but assessment varies between doctors.

Methods: Patients and controls enrolled in the Studies Investigating Co- morbidities Aggravating Heart Failure (SICA) were included in this analysis. JV dimension was measured using a linear high frequency probe (10 MHz) at rest, during a Valsalva manoeuvre and during deep inspiration. Total 200 patients were enrolled: 180 (90%) patients who had heart failure and 20 (10%) controls. VP was measured in 111 patients (55%) who were treated with beta-blocker (100%), angiotensin convert- ing enzyme inhibitor (90%), aldosterone antagonist (20%), diuretics (75%) and 31.1% with statins. Mean age was 64.3±12.5 years, mean ejection fraction was 51.3±5.9, 3.9 (2.7 – 4.9) and 3.2 (2.2 – 4.8) in patients (p=0.005). JVD ratio correlated with log (NTproBNP) (r=−0.29, p=0.003), ejection fraction (EF, r=0.20, p=0.04) and trans-tricuspid systolic gradient (r=−0.39, p<0.001). However, a mul- tivariate model suggested only mitral E/E' and trans-tricuspid gradient were independently associated with JVD ratio (p<0.027). When the analysis was restricted to patients with EF < 40% (n: 45), only higher trans-tricuspid gradient, ar- terial and lower BNP were independently associated with a lower JVD ratio (p<0.05).

Conclusions: A decreased capacity of distension of the jugular veins during Val- salva manoeuvre was a potential biomarker for chronic heart failure, rather than Valsalva ratio. It can be used as an auxiliary parameter in the prognosis in patients with chronic heart failure.

P5165

Artificial neural network in early identification of heart failure progression in OptiVol alert with telemonitoring management of chronic heart failure

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Daily acquisition and analysis of vital sign data and clinical symptoms in chronic heart failure patients allow for early recognition of an emerging decompensation. Artificial Neural Networks (ANN) are a statistical model, which is able to learn probability distributions of a dataset by inductive example training. Here, the ca- pability of a personalized ANN was tested to predict the progression of chronic heart failure in the individual patient.

Methods: In 169 patients hospitalized due to chronic heart failure decompensa- tion, a multiparameter telemonitoring was performed after discharge for up to 3.5 years with 150.000 patient days in total. Daily recording of vital signs (ECG, body- weight, blood pressure (BP), CO saturation, plethysmographic pleth variability, ad- herence, request of contact) generated 1.5 million telemonitoring datapoints, which were used to predict the primary endpoint ‘new heart failure hospitaliza- tion’ per ANN. An ANN to predict the probability of a health state change was trained based on recent vital measurements. Therefore, 80% randomly chosen datapoints of all pa- tients were used to train the ANN (group 1). The remaining 20% were used to test the predictive value of the trained model (group 2). Doing that, the last 7 measure-
Abnormal acetylcholine-induced vasoreactivity in Takotsubo cardiomyopathy, novel pathophysiology insights on Takotsubo cardiomyopathy

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More than 10 years has passed since the first report of Takotsubo Cardiomyopathy (TTC), but our knowledge of this syndrome is still limited. Several hypotheses have been described, but clinical data are still very poor. We sought to test coronary vasoreactivity with administration of intracoronary Acetylcholine (ACH) in patients with TTC. Consecutive patients were prospectively collected in a clinical Registry that involves 3 Hospitals. Since 2011 in one of the 3 Institutions, stable TTC pts were tested with intracoronary administration of acetylcholine (boluses of 4 – 20 – 100 micrograms). Positive test was defined as coronary spasm, with a >75% reduction of the epicardial artery diameter or diffuse vasoconstriction in ≥ 1 vessel with transient slow – no flow. 174 consecutive TTC pts were enrolled in the Registry. A subgroup of 11 patients underwent ACH test. The incidence of abnormal response after ACH administration was 54% (N=6 pts). In 4/5 patients intracoronary ACH induced a focal or multilocal spasm in the left anterior descending artery (LAD). 1 patient developed a diffuse spasm involving also the circumflex artery. 1 patient developed a <50% spasm with transient flow in the LAD. Intra coronary NTG administration promptly reversed the abnormal vasoreactivity in all of the patients.

These data are quite similar to those reported in the CASPAR study that tested intracoronary ACH in patients with acute coronary syndromes and non-significant CAD. In our population prevalence of abnormal coronary vasomotor response to Acetylcholine is high and comparable with that reported in acute coronary syndromes with no CAD. Our findings suggest that abnormal coronary artery vasomotion related to endothelial dysfunction could play a significant pathogenetic role in TTC.

Heart failure symptoms and sleep-disordered breathing in patients with chronic heart failure - results from the SchlaHF-registry

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Objective: In patients with stable chronic heart failure (CHF) we investigated the clinical value of different heart failure symptoms and its relationship to the presence of sleep-disordered breathing (SDB).

Methods: The ongoing multi-center SchlaHF registry documents demographic and clinical data on stable CHF patients. We analyzed the data of 3504 CHF prospectively enrolled patients from cardiology outpatient clinics and practices. Inclusion criteria are New York Heart Association (NYHA) class II – III and left-ventricular ejection fraction (LVEF) ≥ 45%. SDB was determined by a two-channel screening (nasal airflow, pulse oximetry) using ApneaLink (ResMed, Sydney, Australia).

Results: The symptoms analyzed were naptime, nocturnal dyspnea and nocturia. The median naptime was 30 min. In an univariate analysis AHI ≥ 15 (OR = 1.217; CI 1.087-1.400) and ODI ≥ 5 (OR = 1.35; CI 1.155-1.613) were statistically significant (p < 0.05) predictors for a naptime > 30 min while in a logistic regression it wasn’t. There was an increase in nocturia (> 3 times a night) in patients with sdb being in NYHA functional class III and IV depending on severity of sdb, while this could not be seen in patients in NYHA functional class II. A logistic regression analysis for nocturia (> 3 times a night) were AHI=15/h (OR = 1.261; 95% CI 1.048-1.517), NYHA III/IV (OR = 1.467; 95% CI 1.202-1.791), and age (per 10 years increment: OR = 1.328; 95% CI 1.217-1.450). Nocturnal dyspnea increased with severity of sdb in NYHA functional class III and IV and in patients in NYHA functional class II, although being more often seen in the patients with worse functional class. The logistical regression analysis for the presence of nocturnal dyspnea revealed sdb with an AHI=15/h as a significant predictor (OR = 1.583; 95% CI 1.381-1.872). Other significant variables were NYHA III/IV (OR = 1.548; 95% CI 1.291-1.855), age (per 10 years increment: OR = 1.128; 95% CI 1.042-1.216), BMI –30kg/m2 (OR = 1.442; 95% CI 1.208-1.721) and LVEF<25% (OR = 1.624; 95% CI 1.289-2.045).

Conclusions: The multi-center SchlaHF registry shows that HF symptoms are linked to the presence and the severity of SDB. Age and the severity of CHF were other important clinical predictors.

Heart rate control is important even in heart failure patients - an interim analysis of the CHART-2 study

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Purpose: Elevated heart rate (HR) is an independent risk factor for mortality in heart failure (HF) patients. However, the medications for the management of HR often lower systolic blood pressure (SBP) that may worsen the prognosis of HF patients. We examined the importance of HR control in terms of SBP in patients of our Chronic Heart Failure Analysis and Registry in the Tohoku district 2 (CHART-2) Study.

Methods: The CHART-2 Study (N=10,219) is a multicenter prospective cohort study enrolling Stage B/C/D patients. The study subjects were 2,761 overt HF patients with sinus rhythm and divided them into 6 groups based on the tertiles of SBP and the median HR as follows; G1 (SBP ≥ 135 and HR ≥ 70, N=430), G2 (SBP ≥ 135 and HR ≤ 70, N=469), G3 (SBP ≤ 120, HR ≤ 70, N=444), G4 (SBP ≤ 120, HR ≤ 70, N=410), G5 (SBP > 120, HR > 70, N=490), G6 (SBP > 120, HR > 70, N=518).

Results: G3 had the lowest NYHA class and brain natriuretic peptide (BNP) level. On the other hand, G6 were characterized by lower beta-blocker use, lower left ventricular ejection fraction, and the highest BNP level. During a mean follow-up of 3.1 years, non-adjusted Kaplan-Meier curves for all-cause death and cardiovascular death showed that G3 had better prognosis and G6 had poorer prognosis (Figure). In multivariable Cox model including covariates that might influence HR and SBP, Groups with elevated HR showed ~159% increased hazard ratios for all-cause death as compared to G3 (reference). Furthermore, G4 and G6 had significant higher cardiovascular mortality.

Conclusions: Regardless of SBP, elevated HR was associated with higher mortality. In view these results and well-known importance of increased HR for mortality, HR control (<70/min) should be given higher priority even in the HF patients with relatively low SBP.
Incident heart failure with preserved ejection fraction in the general population

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Purpose: The incidence of heart failure (HF) with preserved ejection fraction (HF-PEF) is increasing, compared to HF with reduced ejection fraction (HF-REF). Data on distinctive epidemiology and prediction of incident HF-PEF and HF-REF in a general population have not been described.

Methods: In 8569 HF-free subjects of a general population based cohort study (PREVEND), we studied the performance of established cardiovascular risk factors on incident HF, their hazard ratios given per 1-SD increment and 95% confidence interval (CI), and the additive value of N-terminal pro-B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP) and high-sensitive troponin T (hs-TnT) by c-statistics and net reclassification improvement (NRI). Incident HF was diagnosed by record linkage with databases of regional hospitals. All cases were reviewed and scored as HF-PEF or HF-REF by an independent adjudication committee.

Results: During median follow-up for 10 years, 135 individuals were diagnosed with HF-PEF and 239 with HF-REF. When adjusted for age, sex and body mass index, development of HF-PEF showed strongest associations with hypertension (HR: 2.08, 95% CI: 1.02-4.27, p=0.045), cystatin-C (HR: 1.49, 95% CI: 1.05-2.11, p=0.024) and urinary albumin excretion (HR: 1.37, 95% CI: 1.14-1.65, p=0.001). In similar analyses, development of HF-REF showed strongest associations with history of myocardial infarction (HR: 2.45, 95% CI: 1.53-3.93, p<0.001), smoking (HR: 1.69, 95% CI: 1.07-2.68, p=0.025) and hypercholesterolemia (HR: 1.55, 95% CI: 1.03-2.34, p=0.037). NT-proBNP was independently associated with both incident HF-REF and incident HF-PEF (HR: 1.55, 95% CI: 1.21-1.97, p<0.001 and HR: 1.36, 95% CI: 1.03-1.80, p=0.030, respectively). Hs-TnT was independently associated with incident HF-REF (HR: 1.39, 95% CI: 1.22-1.60, p<0.001), but not with HF-PEF. CRP was not associated with either type of incident HF. For HF-PEF, NT-proBNP, hs-TnT and CRP significantly improved the model c-statistic from 0.85 to 0.86 (p=0.015) and enhanced risk reclassification (NRI=0.06, p=0.048). For HF-REF, the model c-statistic improved from 0.84 to 0.88 (p<0.001) and also enhanced risk reclassification (NRI=0.26, p<0.001).

Conclusions: HF-PEF shows a clear distinctive baseline profile compared to HF-REF, with a blood pressure and renal function pressure-load driven profile for the former and an ischemic driven profile for the latter. The incremental value of biomarkers seems to be less strong for predicting HF-PEF than for HF-REF.